A244

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 March 2005 (24.03.2005)

PCT

(10) International Publication Number
WO 2005/026370 A2

(51) International Patent Classification[7]: C12N 15/86

(21) International Application Number: PCT/US2004/028751

(22) International Filing Date: 3 September 2004 (03.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/500,572 5 September 2003 (05.09.2003) US
60/504,007 18 September 2003 (18.09.2003) US

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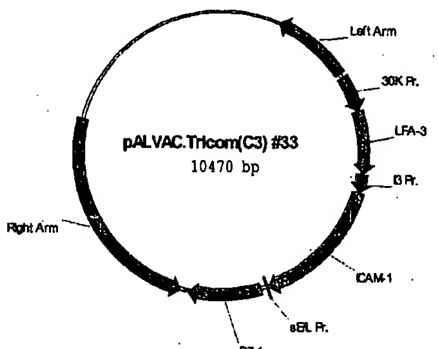
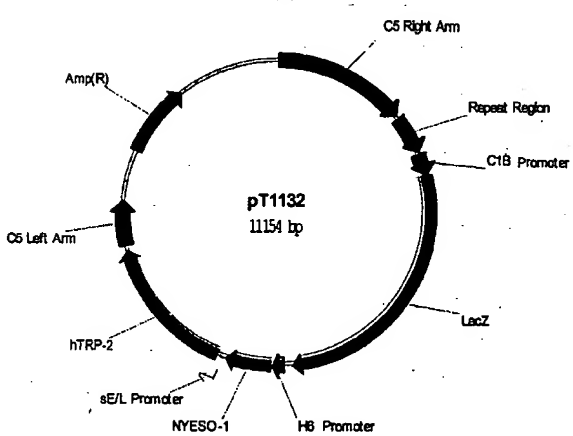
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,

[Continued on next page]

(54) Title: MULTI-ANTIGEN VECTORS FOR MELANOMA





(57) Abstract: The present invention relates to peptides, polypeptides, and nucleic acids and the use of the peptide, polypeptide or nucleic acid in preventing and / or treating cancer. In particular, the invention relates to peptides and nucleic acid sequences encoding such peptides for use in diagnosing, treating, or preventing melanoma.

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GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Multi-Antigen Vectors for Melanoma

FIELD OF THE INVENTION

The present invention relates to multi-antigen vectors for use in preventing and / or treating cancer. In particular, the invention relates to multi-antigen vectors for use in treating and/or preventing melanoma.

BACKGROUND OF THE INVENTION

There has been tremendous increase in last few years in the development of cancer vaccines with tumour-associated antigens (TAAs) due to the great advances in identification of molecules based on the expression profiling on primary tumours and normal cells with the help of several techniques such as high density microarray, SEREX, immunohistochemistry (IHC), RT-PCR, in-situ hybridization (ISH) and laser capture microscopy (Rosenberg, Immunity, 1999; Sgroi et al, 1999, Schena et al, 1995, Offringa et al, 2000). The TAAs are antigens expressed or over-expressed by tumour cells and could be specific to one or several tumours for example CEA antigen is expressed in colorectal, breast and lung cancers. Sgroi et al (1999) identified several genes differentially expressed in invasive and metastatic carcinoma cells with combined use of laser capture microdissection and cDNA microarrays. Several delivery systems like DNA or viruses could be used for therapeutic vaccination against human cancers (Bonnet et al, 2000) and can elicit immune responses and also break immune tolerance against TAAs. Tumour cells can be rendered more immunogenic by inserting transgenes encoding T cell co-stimulatory molecules such as B7.1 or cytokines such as IFN-γ, IL2, or GM-CSF, among others. Co-expression of a TAA and a cytokine or a co-stimulatory molecule can develop effective therapeutic vaccine (Hodge et al, 95, Bronte et al, 1995, Chamberlain et al, 1996).

There is a need in the art for reagents and methodologies useful in stimulating an immune response to prevent or treat cancers. The present invention provides such reagents and methodologies that overcome many of the difficulties encountered by others in attempting to treat cancer.

SUMMARY OF THE INVENTION

The present invention provides multi-antigen vectors for administration to a patient to prevent and / or treat cancer. In particular, the multi-antigen vector encodes one or more tumor antigens ("TA"). The multi-antigen vector may also encode an immune stimulator such as a co-stimulatory molecule and/or be administered with an adjuvant.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Schematic of plasmids pALVAC.Tricom(#33) and pT1132.

Figure 2. DNA sequence of plasmid pALVAC.Tricom(#33).

Figure 3. DNA sequence of plasmid pT1132.

Figure 4. Schematic of plasmid pT3217.

Figure 5. DNA sequence of plasmid pT3217.

Figure 6. Amino acid sequences of exemplary NY-ESO-1, TRP-2, gp100, gp100M, MART-1, MAGE-1, MAGE-3, B7.1, LFA-3, and ICAM-1 proteins.

DETAILED DESCRIPTION

The present invention provides reagents and methodologies useful for treating and / or preventing cancer. All references cited within this application are incorporated by reference.

In one embodiment, the present invention relates to the induction or enhancement of an immune response against one or more tumor antigens ("TA") to prevent and / or treat cancer. In certain embodiments, one or more TAs may be combined. In preferred embodiments, the immune response results from expression of a TA in a host cell following administration of a nucleic acid vector encoding the tumor antigen or the tumor antigen itself in the form of a peptide or polypeptide, for example.

As used herein, an "antigen" is a molecule (such as a polypeptide) or a portion thereof that produces an immune response in a host to whom the antigen has been administered. The immune response may include the production of antibodies that bind to at least one epitope of the antigen and / or the generation of a cellular immune response against cells expressing an epitope of the antigen. The response may be an enhancement of a current immune response by, for example, causing increased antibody production, production of antibodies with increased affinity for the antigen, or an increase in the cellular immune response (i.e., increased number or activity

of immunoreactive T cells). An antigen that produces an immune response may alternatively be referred to as being immunogenic or as an immunogen. In describing the present invention, a TA may be referred to as an "immunogenic target". The present invention provide expression vectors for expressing in a host one or more immunogenic targets.

The term TA includes both tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs), where a cancerous cell is the source of the antigen. A TAA is an antigen that is expressed on the surface of a tumor cell in higher amounts than is observed on normal cells or an antigen that is expressed on normal cells during fetal development. A TSA is an antigen that is unique to tumor cells and is not expressed on normal cells. TA further includes TAAs or TSAs, antigenic fragments thereof, and modified versions that retain their antigenicity.

TAs are typically classified into five categories according to their expression pattern, function, or genetic origin: cancer-testis (CT) antigens (i.e., MAGE, NY-ESO-1); melanocyte differentiation antigens (i.e., Melan A/MART-1, tyrosinase, gp100); mutational antigens (i.e., MUM-1, p53, CDK-4); overexpressed 'self' antigens (i.e., HER-2/neu, p53); and, viral antigens (i.e., HPV, EBV). For the purposes of practicing the present invention, a suitable TA is any TA that induces or enhances an anti-tumor immune response in a host to whom the TA has been administered. Suitable TAs include, for example, species of gp100 (Cox et al., *Science*, 264:716-719 (1994); U.S. Pat. No. 6,500,919 B1 and WO 01/30847 with Val at residue 162, also referred to as "gp100M"; U.S. Pat. No. 6,537,560 B1 with Phe at residue 162), MART-1/Melan A (Kawakami et al., *J. Exp. Med.*, 180:347-352 (1994); U.S. Pat. No. 5,874,560), gp75 (TRP-1) (Wang et al., *J. Exp. Med.*, 186:1131-1140 (1996)), TRP-2 (Wang et al. 1996 J. Exp. Med. 184:2207; U.S. Pat. Nos. 5,831,016 and 6,083,783), tyrosinase (Wolfél et al., *Eur. J. Immunol.*, 24:759-764 (1994); WO 200175117; WO 200175016; WO 200175007), NY-ESO-1 (WO 98/14464; WO 99/18206; GenBank Accession No. P78358; U.S. Pat. No. 5,804,381), melanoma proteoglycan (Hellstrom et al., *J. Immunol.*, 130:1467-1472 (1983)), MAGE family antigens (i.e., MAGE-1, 2,3,4,6,12, 51; Van der Bruggen et al., *Science*, 254:1643-1647 (1991); U.S. Pat. Nos. 6,235,525; CN 1319611), BAGE family antigens (Boel et al., *Immunity*, 2:167-175 (1995)), GAGE family antigens (i.e., GAGE-1,2; Van den Eynde et al., *J. Exp. Med.*, 182:689-698 (1995); U.S. Pat. No. 6,013,765), RAGE family antigens (i.e., RAGE-1; Gaugler et at., *Immunogenetics*, 44:323-330 (1996); U.S. Pat. No. 5,939,526), N-acetylglucosaminyltransferase-V (Guilloux et at., *J. Exp. Med.*, 183:1173-1183 (1996)), p15 (Robbins et al., *J. Immunol.*

154:5944-5950 (1995)), ß-catenin (Robbins et al., *J. Exp. Med.*, 183:1185-1192 (1996)), MUM-1 (Coulie et al., *Proc. Natl. Acad. Sci.* USA, 92:7976-7980 (1995)), cyclin dependent kinase-4 (CDK4) (Wolfel et al., *Science*, 269:1281-1284 (1995)), p21-*ras* (Fossum et at., *Int. J. Cancer*, 56:40-45 (1994)), BCR-*abl* (Bocchia et al., *Blood*, 85:2680-2684 (1995)), p53 (Theobald et al., *Proc. Natl. Acad. Sci.* USA, 92:11993-11997 (1995)), p185 HER2/neu (erb-B1; Fisk et al., *J. Exp. Med.*, 181:2109-2117 (1995)), epidermal growth factor receptor (EGFR) (Harris et al., Breast Cancer Res. Treat, 29:1-2 (1994)), carcinoembryonic antigens (CEA) (Kwong et al., *J. Natl. Cancer Inst.*, 85:982-990 (1995) U.S. Pat. Nos. 5,756,103; 5,274,087; 5,571,710; 6,071,716; 5,698,530; 6,045,802; EP 263933; EP 346710; and, EP 784483); carcinoma-associated mutated mucins (i.e., MUC-1 gene products; Jerome et al., *J. Immunol.*, 151:1654-1662 (1993)); EBNA gene products of EBV (i.e., EBNA-1; Rickinson et al., *Cancer Surveys*, 13:53-80 (1992)); E7, E6 proteins of human papillomavirus (Ressing et al., *J. Immunol*, 154:5934-5943 (1995)); prostate specific antigen (PSA; Xue et al., *The Prostate*, 30:73-78 (1997)); prostate specific membrane antigen (PSMA; Israeli, et al., *Cancer Res.*, 54:1807-1811 (1994)); idiotypic epitopes or antigens, for example, immunoglobulin idiotypes or T cell receptor idiotypes (Chen et al., *J. Immunol.*, 153:4775-4787 (1994)); KSA (U.S. Patent No. 5,348,887), kinesin 2 (Dietz, et al. Biochem Biophys Res Commun 2000 Sep 7;275(3):731-8), HIP-55, TGFβ-1 anti-apoptotic factor (Toomey, et al. Br J Biomed Sci 2001;58(3):177-83), tumor protein D52 (Bryne J.A., et al., Genomics, 35:523-532 (1996)), H1FT, NY-BR-1 (WO 01/47959), NY-BR-62, NY-BR-75, NY-BR-85, NY-BR-87, NY-BR-96 (Scanlan, M. Serologic and Bioinformatic Approaches to the Identification of Human Tumor Antigens, in *Cancer Vaccines 2000*, Cancer Research Institute, New York, NY), including "wild-type" (i.e., normally encoded by the genome, naturally-occurring), modified, and mutated versions as well as other fragments and derivatives thereof. Any of these TAs may be utilized alone or in combination with one another in a co-immunization protocol.

Preferred TAs are useful for inducing an immune response against melanoma cells. The term "melanoma" includes but is not limited to melanomas, metastatic melanomas, melanomas derived from either melanocytes or melanocyte related nevus cells, melanocarcinomas, melanoepitheliomas, melanosarcomas, melanoma *in situ*, superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, acral lentiginous melanoma, invasive melanoma and familial atypical mole and melanoma (FAM-M) syndrome, for example. In general,

melanomas result from chromosomal abnormalities, degenerative growth and development disorders, mitogenic agents, ultraviolet radiation (UV), viral infections, inappropriate tissue expression of a gene, alterations in expression of a gene or carcinogenic agents, for example.

In certain cases, it may be beneficial to co-immunize patients with both TA and other antigens, such as angiogenesis-associated antigens ("AA"). An AA is an immunogenic molecule (i.e., peptide, polypeptide) associated with cells involved in the induction and / or continued development of blood vessels. For example, an AA may be expressed on an endothelial cell ("EC"), which is a primary structural component of blood vessels. Where the cancer is cancer, it is preferred that that the AA be found within or near blood vessels that supply a tumor. Immunization of a patient against an AA preferably results in an anti-AA immune response whereby angiogenic processes that occur near or within tumors are prevented and / or inhibited. Exemplary AAs include, for example, vascular endothelial growth factor (i.e., VEGF; Bernardini, et al. *J. Urol.*, 2001, 166(4): 1275-9; Starnes, et al. *J. Thorac. Cardiovasc. Surg.*, 2001, 122(3): 518-23; Dias, et al. *Blood*, 2002, 99: 2179-2184), the VEGF receptor (i.e., VEGF-R, flk-1/KDR; Starnes, et al. *J. Thorac. Cardiovasc. Surg.*, 2001, 122(3): 518-23), EPH receptors (i.e., EPHA2; Gerety, et al. 1999, *Cell*, 4: 403-414), epidermal growth factor receptor (i.e., EGFR; Ciardeillo, et al. Clin. Cancer Res., 2001, 7(10): 2958-70), basic fibroblast growth factor (i.e., bFGF; Davidson, et al. Clin. Exp. Metastasis 2000,18(6): 501-7; Poon, et al. Am J. Surg., 2001, 182(3):298-304), platelet-derived cell growth factor (i.e., PDGF-B), platelet-derived endothelial cell growth factor (PD-ECGF; Hong, et al. J. Mol. Med., 2001, 8(2):141-8), transforming growth factors (i.e., TGF-α; Hong, et al. J. Mol. Med., 2001, 8(2):141-8), endoglin (Balza, et al. *Int. J. Cancer*, 2001, 94: 579-585), Id proteins (Benezra, R. Trends Cardiovasc. Med., 2001, 11(6):237-41), proteases such as uPA, uPAR, and matrix metalloproteinases (MMP-2, MMP-9; Djonov, et al. J. Pathol., 2001, 195(2):147-55), nitric oxide synthase (Am. J. Ophthalmol., 2001, 132(4):551-6), aminopeptidase (Rouslhati, E. Nature Cancer, 2: 84-90, 2002), thrombospondins (i.e., TSP-1, TSP-2; Alvarez, et al. Gynecol. Oncol., 2001, 82(2):273-8; Seki, et al. Int. J. Oncol., 2001, 19(2):305-10), k-*ras* (Zhang, et al. Cancer Res., 2001, 61(16):6050-4), *Wnt* (Zhang, et al. Cancer Res., 2001, 61(16):6050-4), cyclin-dependent kinases (CDKs; Drug Resist. Updat. 2000, 3(2):83-88), microtubules (Timar, et al. 2001. *Path. Oncol. Res.*, 7(2): 85-94), heat shock proteins (i.e., HSP90 (Timar, *supra*)), heparin-binding factors (i.e., heparinase; Gohji, et al. Int. J. Cancer, 2001, 95(5):295-301), synthases (i.e., ATP synthase,

thymidilate synthase), collagen receptors, integrins (i.e., αυβ3, αυβ5, α1β1, α2β1, α5β1), the surface proteolglycan NG2, AAC2-1, or AAC2-2, among others, including "wild-type" (i.e., normally encoded by the genome, naturally-occurring), modified, mutated versions as well as other fragments and derivatives thereof. Any of these targets may be suitable in practicing the present invention, either alone or in combination with one another or with other agents.

The nucleic acid molecule may comprise or consist of a nucleotide sequence encoding one or more immunogenic targets, or fragments or derivatives thereof, such as that contained in a DNA insert in an ATCC Deposit. The term "nucleic acid sequence" or "nucleic acid molecule" refers to a DNA or RNA sequence. The term encompasses molecules formed from any of the known base analogs of DNA and RNA such as, but not limited to 4-acetylcytosine, 8-hydroxy-N6-methyladenosine, aziridinyl-cytosine, pseudoisocytosine, 5-(carboxyhydroxylmethyl) uracil, 5-fluorouracil, 5-bromouracil, 5-carboxymethylaminomethyl-2-thiouracil, 5-carboxy-methylaminomethyluracil, dihydrouracil, inosine, N6-iso-pentenyladenine, 1-methyladenine, 1-methylpseudouracil, 1-methylguanine, 1-methylinosine, 2,2-dimethyl-guanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-methyladenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyamino-methyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarbonyl-methyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid, oxybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, N-uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid, pseudouracil, queosine, 2-thiocytosine, and 2,6-diaminopurine, among others.

An isolated nucleic acid molecule is one that: (1) is separated from at least about 50 percent of proteins, lipids, carbohydrates, or other materials with which it is naturally found when total nucleic acid is isolated from the source cells; (2) is not be linked to all or a portion of a polynucleotide to which the nucleic acid molecule is linked in nature; (3) is operably linked to a polynucleotide which it is not linked to in nature; and / or, (4) does not occur in nature as part of a larger polynucleotide sequence. Preferably, the isolated nucleic acid molecule of the present invention is substantially free from any other contaminating nucleic acid molecule(s) or other contaminants that are found in its natural environment that would interfere with its use in polypeptide production or its therapeutic, diagnostic, prophylactic or research use. As used herein, the term "naturally occurring" or "native" or "naturally found" when used in connection

with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to materials which are found in nature and are not manipulated by man. Similarly, "non-naturally occurring" or "non-native" as used herein refers to a material that is not found in nature or that has been structurally modified or synthesized by man.

The identity of two or more nucleic acid or amino acid sequences is determined by comparing the sequences. As known in the art, "identity" means the degree of sequence relatedness between nucleic acid or amino acid sequences as determined by the match between the units making up the molecules (i.e., nucleotides or amino acid residues). Identity measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (i.e., an algorithm). Identity between nucleic acid sequences may also be determined by the ability of the nucleic acid sequences to hybridize to one another. In defining the process of hybridization, the term "highly stringent conditions" and "moderately stringent conditions" refer to conditions that permit hybridization of nucleic acid strands whose sequences are complementary, and to exclude hybridization of significantly mismatched nucleic acids. Examples of "highly stringent conditions" for hybridization and washing are 0.015 M sodium chloride, 0.0015 M sodium citrate at 65-68°C or 0.015 M sodium chloride, 0.0015 M sodium citrate, and 50% formamide at 42°C. (see, for example, Sambrook, Fritsch & Maniatis, *Molecular Cloning: A Laboratory Manual* (2nd ed., Cold Spring Harbor Laboratory, 1989); Anderson *et al.*, *Nucleic Acid Hybridisation: A Practical Approach* Ch. 4 (IRL Press Limited)). The term "moderately stringent conditions" refers to conditions under which a DNA duplex with a greater degree of base pair mismatching than could occur under "highly stringent conditions" is able to form. Exemplary moderately stringent conditions are 0.015 M sodium chloride, 0.0015 M sodium citrate at 50-65°C or 0.015 M sodium chloride, 0.0015 M sodium citrate, and 20% formamide at 37-50°C. By way of example, moderately stringent conditions of 50°C in 0.015 M sodium ion will allow about a 21% mismatch. During hybridization, other agents may be included in the hybridization and washing buffers for the purpose of reducing non-specific and/or background hybridization. Examples are 0.1% bovine serum albumin, 0.1% polyvinyl-pyrrolidone, 0.1% sodium pyrophosphate, 0.1% sodium dodecylsulfate, $NaDodSO_4$, (SDS), ficoll, Denhardt's solution, sonicated salmon sperm DNA (or another non-complementary DNA), and dextran sulfate, although other suitable agents can also be used. The concentration and types of these

additives can be changed without substantially affecting the stringency of the hybridization conditions.. Hybridization experiments are usually carried out at pH 6.8-7.4; however, at typical ionic strength conditions, the rate of hybridization is nearly independent of pH.

In preferred embodiments of the present invention, vectors are used to transfer a nucleic acid sequence encoding an immunogenic target to a cell. A vector is any molecule used to transfer a nucleic acid sequence to a host cell. In certain cases, an expression vector is utilized. An expression vector is a nucleic acid molecule that is suitable for transformation of a host cell and contains nucleic acid sequences that direct and / or control the expression of the transferred nucleic acid sequences. Expression includes, but is not limited to, processes such as transcription, translation, and splicing, if introns are present. Expression vectors typically comprise one or more flanking sequences operably linked to a heterologous nucleic acid sequence encoding a polypeptide. Flanking sequences may be homologous (i.e., from the same species and / or strain as the host cell), heterologous (i.e., from a species other than the host cell species or strain), hybrid (i.e., a combination of flanking sequences from more than one source), or synthetic, for example.

A flanking sequence is preferably capable of effecting the replication, transcription and / or translation of the coding sequence and is operably linked to a coding sequence. As used herein, the term operably linked refers to a linkage of polynucleotide elements in a functional relationship. For instance, a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the coding sequence. However, a flanking sequence need not necessarily be contiguous with the coding sequence, so long as it functions correctly.. Thus, for example, intervening untranslated yet transcribed sequences can be present between a promoter sequence and the coding sequence and the promoter sequence may still be considered operably linked to the coding sequence. Similarly, an enhancer sequence may be located upstream or downstream from the coding sequence and affect transcription of the sequence.

In certain embodiments, it is preferred that the flanking sequence is a transcriptional regulatory region that drives high-level gene expression in the target cell. The transcriptional regulatory region may comprise, for example, a promoter, enhancer, silencer, repressor element, or combinations thereof. The transcriptional regulatory region may be either constitutive, tissue-specific, cell-type specific (i.e., the region is drives higher levels of transcription in a one type of tissue or cell as compared to another), or regulatable (i.e., responsive to interaction with a

compound such as tetracycline). The source of a transcriptional regulatory region may be any prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the flanking sequence functions in a cell by causing transcription of a nucleic acid within that cell. A wide variety of transcriptional regulatory regions may be utilized in practicing the present invention.

Suitable transcriptional regulatory regions include the CMV promoter (i.e., the CMV-immediate early promoter); promoters from eukaryotic genes (i.e., the estrogen-inducible chicken ovalbumin gene, the interferon genes, the gluco-corticoid-inducible tyrosine aminotransferase gene, and the thymidine kinase gene); and the major early and late adenovirus gene promoters; the SV40 early promoter region (Bernoist and Chambon, 1981, *Nature* 290:304-10); the promoter contained in the 3' long terminal repeat (LTR) of Rous sarcoma virus (RSV) (Yamamoto, *et al.*, 1980, *Cell* 22:787-97); the herpes simplex virus thymidine kinase (HSV-TK) promoter (Wagner *et al.*, 1981, *Proc. Natl. Acad. Sci. U.S.A.* 78:1444-45); the regulatory sequences of the metallothionine gene (Brinster *et al.*, 1982, *Nature* 296:39-42); prokaryotic expression vectors such as the beta-lactamase promoter (Villa-Kamaroff *et al.*, 1978, *Proc. Natl. Acad. Sci. U.S.A.*, 75:3727-31); or the tac promoter (DeBoer *et al.*, 1983, *Proc. Natl. Acad. Sci. U.S.A.*, 80:21-25). Tissue- and / or cell-type specific transcriptional control regions include, for example, the elastase I gene control region which is active in pancreatic acinar cells (Swift *et al.*, 1984, *Cell* 38:639-46; Ornitz *et al.*, 1986, *Cold Spring Harbor Symp. Quant. Biol.* 50:399-409 (1986); MacDonald, 1987, *Hepatology* 7:425-515); the insulin gene control region which is active in pancreatic beta cells (Hanahan, 1985, *Nature* 315:115-22); the immunoglobulin gene control region which is active in lymphoid cells (Grosschedl *et al.*, 1984, *Cell* 38:647-58; Adames *et al.*, 1985, *Nature* 318:533-38; Alexander *et al.*, 1987, *Mol. Cell. Biol.*, 7:1436-44); the mouse mammary tumor virus control region in testicular, breast, lymphoid and mast cells (Leder *et al.*, 1986, *Cell* 45:485-95); the albumin gene control region in liver (Pinkert *et al.*, 1987, *Genes and Devel.* 1:268-76); the alpha-feto-protein gene control region in liver (Krumlauf *et al.*, 1985, *Mol. Cell. Biol.*, 5:1639-48; Hammer *et al.*, 1987, *Science* 235:53-58); the alpha 1-antitrypsin gene control region in liver (Kelsey *et al.*, 1987, *Genes and Devel.* 1:161-71); the beta-globin gene control region in myeloid cells (Mogram *et al.*, 1985, *Nature* 315:338-40; Kollias *et al.*, 1986, *Cell* 46:89-94); the myelin basic protein gene control region in oligodendrocyte cells in the brain (Readhead *et al.*, 1987, *Cell* 48:703-12); the myosin light chain-2 gene control region in

skeletal muscle (Sani, 1985, *Nature* 314:283-86); the gonadotropic releasing hormone gene control region in the hypothalamus (Mason *et al.*, 1986, *Science* 234:1372-78), and the tyrosinase promoter in melanoma cells (Hart, I. Semin Oncol 1996 Feb;23(1):154-8; Siders, et al. Cancer Gene Ther 1998 Sep-Oct;5(5):281-91), among others. Inducible promoters that are activated in the presence of a certain compound or condition such as light, heat, radiation, tetracycline, or heat shock proteins, for example, may also be utilized (see, for example, WO 00/10612). Other suitable promoters are known in the art.

As described above, enhancers may also be suitable flanking sequences. Enhancers are cis-acting elements of DNA, usually about 10-300 bp in length, that act on the promoter to increase transcription. Enhancers are typically orientation- and position-independent, having been identified both 5' and 3' to controlled coding sequences. Several enhancer sequences available from mammalian genes are known (i.e., globin, elastase, albumin, alpha-feto-protein and insulin). Similarly, the SV40 enhancer, the cytomegalovirus early promoter enhancer, the polyoma enhancer, and adenovirus enhancers are useful with eukaryotic promoter sequences. While an enhancer may be spliced into the vector at a position 5' or 3' to nucleic acid coding sequence, it is typically located at a site 5' from the promoter. Other suitable enhancers are known in the art, and would be applicable to the present invention.

While preparing reagents of the present invention, cells may need to be transfected or transformed. Transfection refers to the uptake of foreign or exogenous DNA by a cell, and a cell has been transfected when the exogenous DNA has been introduced inside the cell membrane. A number of transfection techniques are well known in the art (i.e., Graham *et al.*, 1973, *Virology* 52:456; Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (Cold Spring Harbor Laboratories, 1989); Davis *et al.*, *Basic Methods in Molecular Biology* (Elsevier, 1986); and Chu *et al.*, 1981, *Gene* 13:197). Such techniques can be used to introduce one or more exogenous DNA moieties into suitable host cells.

In certain embodiments, it is preferred that transfection of a cell results in transformation of that cell. A cell is transformed when there is a change in a characteristic of the cell, being transformed when it has been modified to contain a new nucleic acid. Following transfection, the transfected nucleic acid may recombine with that of the cell by physically integrating into a chromosome of the cell, may be maintained transiently as an episomal element without being

replicated, or may replicate independently as a plasmid. A cell is stably transformed when the nucleic acid is replicated with the division of the cell.

The expression vectors of the present invention also provide for expression of fragments of immunogenic targets. Fragments may include sequences truncated at the amino terminus (with or without a leader sequence) and / or the carboxy terminus. Fragments may also include variants (i.e., allelic, splice), orthologs, homologues, and other variants having one or more amino acid additions or substitutions or internal deletions as compared to the parental sequence. In preferred embodiments, truncations and/or deletions comprise about 1-5 amino acids, 5-10 amino acids, 10-20 amino acids, 20-30 amino acids, 30-40 amino acids, 40-50 amino acids, or more. Such polypeptide fragments may optionally comprise an amino terminal methionine residue. It will be appreciated that such fragments can be used, for example, to generate antibodies or cellular immune responses to immunogenic targets.

A variant is a sequence having one or more sequence substitutions, deletions, and/or additions as compared to the subject sequence. Variants may be naturally occurring or artificially constructed. Such variants may be prepared from the corresponding nucleic acid molecules. In preferred embodiments, the variants have from 1 to 3, or from 1 to 5, or from 1 to 10, or from 1 to 15, or from 1 to 20, or from 1 to 25, or from 1 to 30, or from 1 to 40, or from 1 to 50, or more than 50 amino acid substitutions, insertions, additions and/or deletions.

An allelic variant is one of several possible naturally-occurring alternate forms of a sequence occupying a given locus on a chromosome of an organism or a population of organisms. A splice variant is a polypeptide generated from one of several RNA transcript resulting from splicing of a primary transcript. An ortholog is a similar nucleic acid or polypeptide sequence from another species. For example, the mouse and human versions of an immunogenic target may be considered orthologs of each other. A derivative of a sequence is one that is derived from a parental sequence those sequences having substitutions, additions, deletions, or chemically modified variants. Variants may also include fusion proteins, which refers to the fusion of one or more first sequences (such as a peptide) at the amino or carboxy terminus of at least one other sequence (such as a heterologous peptide).

"Similarity" is a concept related to identity, except that similarity refers to a measure of relatedness which includes both identical matches and conservative substitution matches. If two polypeptide sequences have, for example, 10/20 identical amino acids, and the remainder are all

non-conservative substitutions, then the percent identity and similarity would both be 50%. If in the same example, there are five more positions where there are conservative substitutions, then the percent identity remains 50%, but the percent similarity would be 75% (15/20). Therefore, in cases where there are conservative substitutions, the percent similarity between two polypeptides will be higher than the percent identity between those two polypeptides.

Substitutions may be conservative, or non-conservative, or any combination thereof. Conservative amino acid modifications to the sequence of a polypeptide (and the corresponding modifications to the encoding nucleotides) may produce polypeptides having functional and chemical characteristics similar to those of a parental polypeptide. For example, a "conservative amino acid substitution" may involve a substitution of a native amino acid residue with a non-native residue such that there is little or no effect on the size, polarity, charge, hydrophobicity, or hydrophilicity of the amino acid residue at that position and, in particlar, does not result in decreased immunogenicity. Suitable conservative amino acid substitutions are shown in **Table I**.

Table I

Original Residues	Exemplary Substitutions	Preferred Substitutions
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

A skilled artisan will be able to determine suitable variants of an immunogenic target using well-known techniques. For identifying suitable areas of the molecule that may be changed without destroying biological activity (i.e., MHC binding, immunogenicity), one skilled in the art may target areas not believed to be important for that activity. For example, when immunogenic targets with similar activities from the same species or from other species are known, one skilled in the art may compare the amino acid sequence of a polypeptide to such similar polypeptides. By performing such analyses, one can identify residues and portions of the molecules that are conserved. It will be appreciated that changes in areas of the molecule that are not conserved relative to such similar immunogenic targets would be less likely to adversely affect the biological activity and/or structure of a polypeptide. Similarly, the residues required for binding to MHC are known, and may be modified to improve binding. However, modifications resulting in decreased binding to MHC will not be appropriate in most situations. One skilled in the art would also know that, even in relatively conserved regions, one may substitute chemically similar amino acids for the naturally occurring residues while retaining activity. Therefore, even areas that may be important for biological activity or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the structure of the immunogenic target.

Other preferred polypeptide variants include glycosylation variants wherein the number and/or type of glycosylation sites have been altered compared to the subject amino acid sequence. In one embodiment, polypeptide variants comprise a greater or a lesser number of N-linked glycosylation sites than the subject amino acid sequence. An N-linked glycosylation site is characterized by the sequence Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X may be any amino acid residue except proline. The substitution of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions that eliminate this sequence will remove an existing N-linked carbohydrate chain. Also provided is a rearrangement of N-linked carbohydrate chains wherein one or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created. To affect O-linked glycosylation of a polypeptide, one would modify serine and / or threonine residues.

Additional preferred variants include cysteine variants, wherein one or more cysteine residues are deleted or substituted with another amino acid (*e.g.*, serine) as compared to the subject amino acid sequence set. Cysteine variants are useful when peptides or polypeptides must be refolded into a biologically active conformation such as after the isolation of insoluble inclusion bodies. Cysteine variants generally have fewer cysteine residues than the native protein, and typically have an even number to minimize interactions resulting from unpaired cysteines.

In other embodiments, the peptides or polypeptides may be attached to one or more fusion segments that assist in purification of the polypeptides. Fusions can be made either at the amino terminus or at the carboxy terminus of the subject polypeptide variant thereof. Fusions may be direct with no linker or adapter molecule or may be through a linker or adapter molecule. A linker or adapter molecule may be one or more amino acid residues, typically from about 20 to about 50 amino acid residues. A linker or adapter molecule may also be designed with a cleavage site for a DNA restriction endonuclease or for a protease to allow for the separation of the fused moieties. It will be appreciated that once constructed, the fusion polypeptides can be derivatized according to the methods described herein. Suitable fusion segments include, among others, metal binding domains (e.g., a poly-histidine segment), immunoglobulin binding domains (i.e., Protein A, Protein G, T cell, B cell, Fc receptor, or complement protein antibody-binding domains), sugar binding domains (e.g., a maltose binding domain), and/or a "tag" domain (i.e., at least a portion of α-galactosidase, a strep tag peptide, a T7 tag peptide, a FLAG peptide, or other domains that can be purified using compounds that bind to the domain, such as monoclonal antibodies). This tag is typically fused to the peptide or polypeptide and upon expression may serve as a means for affinity purification of the sequence of interest polypeptide from the host cell. Affinity purification can be accomplished, for example, by column chromatography using antibodies against the tag as an affinity matrix. Optionally, the tag can subsequently be removed from the purified sequence of interest polypeptide by various means such as using certain peptidases for cleavage. As described below, fusions may also be made between a TA and a co-stimulatory components such as the chemokines CXC10 (IP-10), CCL7 (MCP-3), or CCL5 (RANTES), for example.

A fusion motif may enhance transport of an immunogenic target to an MHC processing compartment, such as the endoplasmic reticulum. These sequences, referred to as tranduction or

transcytosis sequences, include sequences derived from HIV tat (see Kim et al. 1997 J. Immunol. 159:1666), *Drosophila* antennapedia (see Schutze-Redelmeier et al. 1996 J. Immunol. 157:650), or human period-1 protein (hPER1; in particular, SRRHHCRSKAKRSRHH).

In addition, the polypeptide or variant thereof may be fused to a homologous peptide or polypeptide to form a homodimer or to a heterologous peptide or polypeptide to form a heterodimer. Heterologous peptides and polypeptides include, but are not limited to an epitope to allow for the detection and/or isolation of a fusion polypeptide; a transmembrane receptor protein or a portion thereof, such as an extracellular domain or a transmembrane and intracellular domain; a ligand or a portion thereof which binds to a transmembrane receptor protein; an enzyme or portion thereof which is catalytically active; a polypeptide or peptide which promotes oligomerization, such as a leucine zipper domain; a polypeptide or peptide which increases stability, such as an immunoglobulin constant region; a peptide or polypeptide which has a therapeutic activity different from the peptide or polypeptide; and/or variants thereof.

In certain embodiments, it may be advantageous to combine a nucleic acid sequence encoding an immunogenic target with one or more co-stimulatory component(s) such as cell surface proteins, cytokines or chemokines in a composition of the present invention. The co-stimulatory component may be included in the composition as a polypeptide or as a nucleic acid encoding the polypeptide, for example. Suitable co-stimulatory molecules include, for instance, polypeptides that bind members of the CD28 family (i.e., CD28, ICOS; Hutloff, et al. *Nature* 1999, 397: 263–265; Peach, et al. *J Exp Med* 1994, 180: 2049–2058) such as the CD28 binding polypeptides B7.1 (CD80; Schwartz, 1992; Chen et al, 1992; Ellis, et al. *J. Immunol.*, 156(8): 2700-9), B7.2 (CD86; Ellis, et al. *J. Immunol.*, 156(8): 2700-9), and mutants / variants thereof (WO 00/66162); polypeptides which bind members of the integrin family (i.e., LFA-1 (CD11a / CD18); Sedwick, et al. *J Immunol* 1999, 162: 1367–1375; Wülfing, et al. *Science* 1998, 282: 2266–2269; Lub, et al. *Immunol Today* 1995, 16: 479–483) including members of the ICAM family (i.e., ICAM-1, -2 or -3); polypeptides which bind CD2 family members (i.e., CD2, signalling lymphocyte activation molecule (CDw150 or "SLAM"; Aversa, et al. *J Inmunol* 1997, 158: 4036–4044)) such as CD58 (LFA-3; CD2 ligand; Davis, et al. *Immunol Today* 1996, 17: 177–187) or SLAM ligands (Sayos, et al. *Nature* 1998, 395: 462–469); polypeptides which bind heat stable antigen (HSA or CD24; Zhou, et al. *Eur J Immunol* 1997, 27: 2524–2528); polypeptides which bind to members of the TNF receptor (TNFR) family (i.e.,

4-1BB (CD137; Vinay, et al. *Semin Immunol* 1998, 10: 481–489), OX40 (CD134; Weinberg, et al. *Semin Immunol* 1998, 10: 471–480; Higgins, et al. *J Immunol* 1999, 162: 486–493), and CD27 (Lens, et al. *Semin Immunol* 1998, 10: 491–499)) such as 4-1BBL (4-1BB ligand; Vinay, et al. *Semin Immunol* 1998, 10: 481–48; DeBenedette, et al. *J Immunol* 1997, 158: 551–559), TNFR associated factor-1 (TRAF-1; 4-1BB ligand; Saoulli, et al. *J Exp Med* 1998, 187: 1849–1862, Arch, et al. *Mol Cell Biol* 1998, 18: 558–565), TRAF-2 (4-1BB and OX40 ligand; Saoulli, et al. *J Exp Med* 1998, 187: 1849–1862; Oshima, et al. *Int Immunol* 1998, 10: 517–526, Kawamata, et al. *J Biol Chem* 1998, 273: 5808–5814), TRAF-3 (4-1BB and OX40 ligand; Arch, et al. *Mol Cell Biol* 1998, 18: 558–565; Jang, et al. *Biochem Biophys Res Commun* 1998, 242: 613–620; Kawamata S, et al. *J Biol Chem* 1998, 273: 5808–5814), OX40L (OX40 ligand; Gramaglia, et al. *J Immunol* 1998, 161: 6510–6517), TRAF-5 (OX40 ligand; Arch, et al. *Mol Cell Biol* 1998, 18: 558–565; Kawamata, et al. *J Biol Chem* 1998, 273: 5808–5814), and CD70 (CD27 ligand; Couderc, et al. *Cancer Gene Ther.*, 5(3): 163-75). CD154 (CD40 ligand or "CD40L"; Gurunathan, et al. *J. Immunol.*, 1998, 161: 4563-4571; Sine, et al. *Hum. Gene Ther.*, 2001, 12: 1091-1102) may also be suitable.

One or more cytokines may also be suitable co-stimulatory components or "adjuvants", either as polypeptides or being encoded by nucleic acids contained within the compositions of the present invention (Parmiani, et al. Immunol Lett 2000 Sep 15; 74(1): 41-4; Berzofsky, et al. Nature Immunol. 1: 209-219). Suitable cytokines include, for example, interleukin-2 (IL-2) (Rosenberg, et al. *Nature Med.* 4: 321-327 (1998)), IL-4, IL-7, IL-12 (reviewed by Pardoll, 1992; Harries, et al. J. Gene Med. 2000 Jul-Aug;2(4):243-9; Rao, et al. *J. Immunol.* 156: 3357-3365 (1996)), IL-15 (Xin, et al. *Vaccine*, 17:858-866, 1999), IL-16 (Cruikshank, et al. J. Leuk Biol. 67(6): 757-66, 2000), IL-18 (*J. Cancer Res. Clin. Oncol.* 2001. 127(12): 718-726), GM-CSF (CSF (Disis, et al. *Blood*, 88: 202-210 (1996)), tumor necrosis factor-alpha (TNF-α), or interferons such as IFN-α or INF-γ. Other cytokines may also be suitable for practicing the present invention, as is known in the art.

Chemokines may also be utilized, in either polypeptide or nucleic acid form. Fusion proteins comprising CXCL10 (IP-10) and CCL7 (MCP-3) fused to a tumor self-antigen have been shown to induce anti-tumor immunity (Biragyn, et al. *Nature Biotech.* 1999, 17: 253-258). The chemokines CCL3 (MIP-1α) and CCL5 (RANTES) (Boyer, et al. *Vaccine*, 1999, 17 (Supp.

2): S53-S64) may also be of use in practicing the present invention. Other suitable chemokines are known in the art.

It is also known in the art that suppressive or negative regulatory immune mechanisms may be blocked, resulting in enhanced immune responses. For instance, treatment with anti-CTLA-4 (Shrikant, et al. *Immunity*, 1996, 14: 145-155; Sutmuller, et al. *J. Exp. Med.*, 2001, 194: 823-832), anti-CD25 (Sutmuller, *supra*), anti-CD4 (Matsui, et al. *J. Immunol.*, 1999, 163: 184-193), the fusion protein IL13Ra2-Fc (Terabe, et al. *Nature Immunol.*, 2000, 1: 515-520), and combinations thereof (i.e., anti-CTLA-4 and anti-CD25, Sutmuller, *supra*) have been shown to upregulate anti-tumor immune responses and would be suitable in practicing the present invention. Such treatments, among others, may also be combined with the one or more immunogenic targets of the present invention.

Any of these components may be used alone or in combination with other agents. For instance, it has been shown that a combination of CD80, ICAM-1 and LFA-3 ("TRICOM") may potentiate anti-cancer immune responses (Hodge, et al. *Cancer Res.* 59: 5800-5807 (1999). Other effective combinations include, for example, IL-12 + GM-CSF (Ahlers, et al. *J. Immunol.*, 158: 3947-3958 (1997); Iwasaki, et al. *J. Immunol.* 158: 4591-4601 (1997)), IL-12 + GM-CSF + TNF-α (Ahlers, et al. *Int. Immunol.* 13: 897-908 (2001)), CD80 + IL-12 (Fruend, et al. *Int. J. Cancer*, 85: 508-517 (2000); Rao, et al. *supra*), and CD86 + GM-CSF + IL-12 (Iwasaki, supra). One of skill in the art would be aware of additional combinations useful in carrying out the present invention. In addition, the skilled artisan would be aware of additional reagents or methods that may be used to modulate such mechanisms. These reagents and methods, as well as others known by those of skill in the art, may be utilized in practicing the present invention.

Additional strategies for improving the efficiency of nucleic acid-based immunization may also be used including, for example, the use of self-replicating viral replicons (Caley, et al. 1999. *Vaccine*, 17: 3124-2135; Dubensky, et al. 2000. *Mol. Med.* 6: 723-732; Leitner, et al. 2000. *Cancer Res.* 60: 51-55), codon optimization (Liu, et al. 2000. *Mol. Ther.*, 1: 497-500; Dubensky, *supra*; Huang, et al. 2001. *J. Virol.* 75: 4947-4951), *in vivo* electroporation (Widera, et al. 2000. *J. Immunol.* 164: 4635-3640), incorporation of CpG stimulatory motifs (Gurunathan, et al. *Ann. Rev. Immunol.*, 2000, 18: 927-974; Leitner, *supra*; Cho, et al. J. Immunol. 168(10):4907-13), sequences for targeting of the endocytic or ubiquitin-processing pathways (Thomson, et al. 1998. *J. Virol.* 72: 2246-2252; Velders, et al. 2001. *J. Immunol.*

166: 5366-5373), Marek's disease virus type 1 VP22 sequences (J. Virol. 76(6):2676-82, 2002), prime-boost regimens (Gurunathan, *supra*; Sullivan, et al. 2000. *Nature*, 408: 605-609; Hanke, et al. 1998. *Vaccine*, 16: 439-445; Amara, et al. 2001. *Science*, 292: 69-74), and the use of mucosal delivery vectors such as *Salmonella* (Darji, et al. 1997. *Cell*, 91: 765-775; Woo, et al. 2001. *Vaccine*, 19: 2945-2954). Other methods are known in the art, some of which are described below.

Chemotherapeutic agents, radiation, anti-angiogenic compounds, or other agents may also be utilized in treating and / or preventing cancer using immunogenic targets (Sebti, et al. Oncogene 2000 Dec 27;19(56):6566-73). For example, in treating metastatic melanoma, suitable chemotherapeutic regimens may include BELD (bleomycin, vindesine, lomustine, and deacarbazine; Young, et al. 1985. Cancer, 55: 1879-81), BOLD (bleomycin, vincristine, lomustine, dacarbazine; Seigler, et al. 1980. Cancer, 46 : 2346-8) ; DD (dacarbazine, actinomycin ; Hochster, et al. Cancer Treatment Reports, 69: 39-42), or POC (procarbazine, vincristine, lomustine; Carmo-Pereira, et al. 1984. Cancer Treatment Reports, 68: 1211-4) among others. Other suitable chemotherapeutic regimens may also be utilized.

Many anti-angiogenic agents are known in the art and would be suitable for co-administration with the immunogenic target vaccines and/or chemotherapeutic regimens (see, for example, Timar, et al. 2001. *Pathology Oncol. Res.*, 7(2): 85-94). Such agents include, for example, physiological agents such as growth factors (i.e., ANG-2, NK1,2,4 (HGF), transforming growth factor beta (TGF-β)), cytokines (i.e., interferons such as IFN-α, -β, -γ, platelet factor 4 (PF-4), PR-39), proteases (i.e., cleaved AT-III, collagen XVIII fragment (Endostatin)), HmwKallikrein-d5 plasmin fragment (Angiostatin), prothrombin-F1-2, TSP-1), protease inhibitors (i.e., tissue inhibitor of metalloproteases such as TIMP-1, -2, or –3; maspin; plasminogen activator-inhibitors such as PAI-1; pigment epithelium derived factor (PEDF)), Tumstatin (available through ILEX, Inc.), antibody products (i.e., the collagen-binding antibodies HUIV26, HUI77, XL313; anti-VEGF; anti-integrin (i.e., Vitaxin, (Lxsys))), and glycosidases (i.e., heparinase-I, -III). "Chemical" or modified physiological agents known or believed to have anti-angiogenic potential include, for example, vinblastine, taxol, ketoconazole, thalidomide, dolestatin, combrestatin A, rapamycin (Guba, et al. 2002, *Nature Med.*, 8: 128-135), CEP-7055 (available from Cephalon, Inc.), flavone acetic acid, Bay 12-9566 (Bayer Corp.), AG3340 (Agouron, Inc.), CGS 27023A (Novartis), tetracylcine derivatives (i.e., COL-3

(Collagenix, Inc.)), Neovastat (Aeterna), BMS-275291 (Bristol-Myers Squibb), low dose 5-FU, low dose methotrexate (MTX), irsofladine, radicicol, cyclosporine, captopril, celecoxib, D45152-sulphated polysaccharide, cationic protein (Protamine), cationic peptide-VEGF, Suramin (polysulphonated napthyl urea), compounds that interfere with the function or production of VEGF (i.e., SU5416 or SU6668 (Sugen), PTK787/ZK22584 (Novartis)), Distamycin A, Angiozyme (ribozyme), isoflavinoids, staurosporine derivatives, genistein, EMD121974 (Merck KcgaA), tyrphostins, isoquinolones, retinoic acid, carboxyamidotriazole, TNP-470, octreotide, 2-methoxyestradiol, aminosterols (i.e., squalamine), glutathione analogues (i.e., N-acteyl-L-cysteine), combretastatin A-4 (Oxigene), Eph receptor blocking agents (*Nature*, 414:933-938, 2001), Rh-Angiostatin, Rh-Endostatin (WO 01/93897), cyclic-RGD peptide, accutin-disintegrin, benzodiazepenes, humanized anti-avb3 Ab, Rh-PAI-2, amiloride, p-amidobenzamidine, anti-uPA ab, anti-uPAR Ab, L-phanylalanin-N-methylamides (i.e., Batimistat, Marimastat), AG3340, and minocycline. Many other suitable agents are known in the art and would suffice in practicing the present invention.

The present invention may also be utilized in combination with "non-traditional" methods of treating cancer. For example, it has recently been demonstrated that administration of certain anaerobic bacteria may assist in slowing tumor growth. In one study, *Clostridium novyi* was modified to eliminate a toxin gene carried on a phage episome and administered to mice with colorectal tumors (Dang, et al. *P.N.A.S. USA*, 98(26): 15155-15160, 2001). In combination with chemotherapy, the treatment was shown to cause tumor necrosis in the animals. The reagents and methodologies described in this application may be combined with such treatment methodologies.

Nucleic acids encoding immunogenic targets may be administered to patients by any of several available techniques. Various viral vectors that have been successfully utilized for introducing a nucleic acid to a host include retrovirus, adenovirus, adeno-associated virus (AAV), herpes virus, and poxvirus, among others. It is understood in the art that many such viral vectors are available in the art. The vectors of the present invention may be constructed using standard recombinant techniques widely available to one skilled in the art. Such techniques may be found in common molecular biology references such as *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press,

San Diego, CA), and *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA).

Preferred retroviral vectors are derivatives of lentivirus as well as derivatives of murine or avian retroviruses. Examples of suitable retroviral vectors include, for example, Moloney murine leukemia virus (MoMuLV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), SIV, BIV, HIV and Rous Sarcoma Virus (RSV). A number of retroviral vectors can incorporate multiple exogenous nucleic acid sequences. As recombinant retroviruses are defective, they require assistance in order to produce infectious vector particles. This assistance can be provided by, for example, helper cell lines encoding retrovirus structural genes. Suitable helper cell lines include Ψ2, PA317 and PA12, among others. The vector virions produced using such cell lines may then be used to infect a tissue cell line, such as NIH 3T3 cells, to produce large quantities of chimeric retroviral virions. Retroviral vectors may be administered by traditional methods (i.e., injection) or by implantation of a "producer cell line" in proximity to the target cell population (Culver, K., *et al.*, 1994, *Hum. Gene Ther.*, 5 (3): 343-79; Culver, K., *et al.*, *Cold Spring Harb. Symp. Quant. Biol.*, 59: 685-90); Oldfield, E., 1993, *Hum. Gene Ther.*, 4 (1): 39-69). The producer cell line is engineered to produce a viral vector and releases viral particles in the vicinity of the target cell. A portion of the released viral particles contact the target cells and infect those cells, thus delivering a nucleic acid of the present invention to the target cell. Following infection of the target cell, expression of the nucleic acid of the vector occurs.

Adenoviral vectors have proven especially useful for gene transfer into eukaryotic cells (Rosenfeld, M., *et al.*, 1991, *Science*, 252 (5004): 431-4; Crystal, R., *et al.*, 1994, *Nat. Genet.*, 8 (1): 42-51), the study eukaryotic gene expression (Levrero, M., *et al.*, 1991, *Gene*, 101 (2): 195-202), vaccine development (Graham, F. and Prevec, L., 1992, *Biotechnology*, 20: 363-90), and in animal models (Stratford-Perricaudet, L., *et al.*, 1992, *Bone Marrow Transplant.*, 9 (Suppl. 1): 151-2 ; Rich, D., *et al.*, 1993, *Hum. Gene Ther.*, 4 (4): 461-76). Experimental routes for administrating recombinant Ad to different tissues *in vivo* have included intratracheal instillation (Rosenfeld, M., *et al.*, 1992, *Cell*, 68 (1): 143-55) injection into muscle (Quantin, B., *et al.*, 1992, *Proc. Natl. Acad. Sci. U.S.A.*, 89 (7): 2581-4), peripheral intravenous injection (Herz, J., and Gerard, R., 1993, *Proc. Natl. Acad. Sci. U.S.A.*, 90 (7): 2812-6) and stereotactic inoculation to brain (Le Gal La Salle, G., *et al.*, 1993, *Science*, 259 (5097): 988-90), among others.

Adeno-associated virus (AAV) demonstrates high-level infectivity, broad host range and specificity in integrating into the host cell genome (Hermonat, P., et al., 1984, *Proc. Natl. Acad. Sci. U.S.A.,* 81 (20): 6466-70). And Herpes Simplex Virus type-1 (HSV-1) is yet another attractive vector system, especially for use in the nervous system because of its neurotropic property (Geller, A., *et al.,* 1991, *Trends Neurosci.,* 14 (10): 428-32; Glorioso, *et al.*, 1995, *Mol. Biotechnol.,* 4 (1): 87-99; Glorioso, *et al.*, 1995, *Annu. Rev. Microbiol.,* 49: 675-710).

Poxvirus is another useful expression vector (Smith, et al. 1983, *Gene,* 25 (1): 21-8; Moss, et al, 1992, *Biotechnology,* 20: 345-62; Moss, et al, 1992, *Curr. Top. Microbiol. Immunol.,* 158: 25-38; Moss, et al. 1991. *Science*, 252: 1662-1667). Poxviruses shown to be useful include vaccinia, NYVAC, avipox, fowlpox, canarypox, ALVAC, and ALVAC(2), among others.

NYVAC (vP866) was derived from the Copenhagen vaccine strain of vaccinia virus by deleting six nonessential regions of the genome encoding known or potential virulence factors (see, for example, U.S. Pat. Nos. 5,364,773 and 5,494,807). The deletion loci were also engineered as recipient loci for the insertion of foreign genes. The deleted regions are: thymidine kinase gene (TK; J2R); hemorrhagic region (u; B13R+B14R); A type inclusion body region (ATI; A26L); hemagglutinin gene (HA; A56R); host range gene region (C7L-K1L); and, large subunit, ribonucleotide reductase (I4L). NYVAC is a genetically engineered vaccinia virus strain that was generated by the specific deletion of eighteen open reading frames encoding gene products associated with virulence and host range. NYVAC has been show to be useful for expressing TAs (see, for example, U.S. Pat. No. 6,265,189). NYVAC (vP866), vP994, vCP205, vCP1433, placZH6H4Lreverse, pMPC6H6K3E3 and pC3H6FHVB were also deposited with the ATCC under the terms of the Budapest Treaty, accession numbers VR-2559, VR-2558, VR-2557, VR-2556, ATCC-97913, ATCC-97912, and ATCC-97914, respectively.

ALVAC-based recombinant viruses (i.e., ALVAC-1 and ALVAC-2) are also suitable for use in practicing the present invention (see, for example, U.S. Pat. No. 5,756,103). ALVAC(2) is identical to ALVAC(1) except that ALVAC(2) genome comprises the vaccinia E3L and K3L genes under the control of vaccinia promoters (U.S. Pat. No. 6,130,066; Beattie et al., 1995a, 1995b, 1991; Chang et al., 1992; Davies et al., 1993). Both ALVAC(1) and ALVAC(2) have been demonstrated to be useful in expressing foreign DNA sequences, such as TAs (Tartaglia et al., 1993 a,b; U.S. Pat. No. 5,833,975). ALVAC was deposited under the terms of the Budapest

Treaty with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Va. 20110-2209, USA, ATCC accession number VR-2547.

Another useful poxvirus vector is TROVAC. TROVAC refers to an attenuated fowlpox that was a plaque-cloned isolate derived from the FP-1 vaccine strain of fowlpoxvirus which is licensed for vaccination of 1 day old chicks. TROVAC was likewise deposited under the terms of the Budapest Treaty with the ATCC, accession number 2553.

"Non-viral" plasmid vectors may also be suitable in practicing the present invention. Preferred plasmid vectors are compatible with bacterial, insect, and / or mammalian host cells. Such vectors include, for example, PCR-II, pCR3, and pcDNA3.1 (Invitrogen, San Diego, CA), pBSII (Stratagene, La Jolla, CA), pET15 (Novagen, Madison, WI), pGEX (Pharmacia Biotech, Piscataway, NJ), pEGFP-N2 (Clontech, Palo Alto, CA), pETL (BlueBacII, Invitrogen), pDSR-alpha (PCT pub. No. WO 90/14363) and pFastBacDual (Gibco-BRL, Grand Island, NY) as well as Bluescript® plasmid derivatives (a high copy number COLE1-based phagemid, Stratagene Cloning Systems, La Jolla, CA), PCR cloning plasmids designed for cloning Taq-amplified PCR products (*e.g.*, TOPO™ TA cloning® kit, PCR2.1® plasmid derivatives, Invitrogen, Carlsbad, CA). Bacterial vectors may also be used with the current invention. These vectors include, for example, *Shigella, Salmonella, Vibrio cholerae, Lactobacillus, Bacille calmette guérin (BCG), and Streptococcus* (see for example, WO 88/6626; WO 90/0594; WO 91/13157; WO 92/1796; and WO 92/21376). Many other non-viral plasmid expression vectors and systems are known in the art and could be used with the current invention.

Suitable nucleic acid delivery techniques include DNA-ligand complexes, adenovirus-ligand-DNA complexes, direct injection of DNA, $CaPO_4$ precipitation, gene gun techniques, electroporation, and colloidal dispersion systems, among others. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. The preferred colloidal system of this invention is a liposome, which are artificial membrane vesicles useful as delivery vehicles *in vitro* and *in vivo*. RNA, DNA and intact virions can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, R., *et al.*, 1981, *Trends Biochem. Sci.*, 6: 77). The composition of the liposome is usually a combination of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in

combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations. Examples of lipids useful in liposome production include phosphatidyl compounds, such as phosphatidylglycerol, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, sphingolipids, cerebrosides, and gangliosides. Particularly useful are diacylphosphatidylglycerols, where the lipid moiety contains from 14-18 carbon atoms, particularly from 16-18 carbon atoms, and is saturated. Illustrative phospholipids include egg phosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.

An immunogenic target may also be administered in combination with one or more adjuvants to boost the immune response. Exemplary adjuvants are shown in Table II below:

Table II

Types of Immunologic Adjuvants

Type of Adjuvant	General Examples	Specific Examples/References
Gel-type	Aluminum hydroxide/phosphate ("alum adjuvants")	(Aggerbeck and Heron, 1995)
	Calcium phosphate	(Relyveld, 1986)
Microbial	Muramyl dipeptide (MDP)	(Chedid et al., 1986)
	Bacterial exotoxins	Cholera toxin (CT), *E.coli* labile toxin (LT)(Freytag and Clements, 1999)
	Endotoxin-based adjuvants	Monophosphoryl lipid A (MPL) (Ulrich and Myers, 1995)
	Other bacterial	CpG oligonucleotides (Corral and Petray, 2000), BCG sequences (Krieg, et al. *Nature*, 374:576), tetanus toxoid (Rice, et al. *J. Immunol.*, 2001, 167: 1558-1565)
Particulate	Biodegradable Polymer microspheres	(Gupta et al., 1998)
	Immunostimulatory complexes (ISCOMs)	(Morein and Bengtsson, 1999)
	Liposomes	(Wassef et al., 1994)
Oil-emulsion and surfactant-based adjuvants	Freund's incomplete adjuvant	(Jensen et al., 1998)
	Microfluidized emulsions	MF59 (Ott et al., 1995)
		SAF (Allison and Byars, 1992) (Allison, 1999)
	Saponins	QS-21 (Kensil, 1996)
Synthetic	Muramyl peptide derivatives	Murabutide (Lederer, 1986) Threony-MDP (Allison, 1997)
	Nonionic block copolymers	L121 (Allison, 1999)
	Polyphosphazene (PCPP)	(Payne et al., 1995)

	Synthetic polynucleotides	Poly A:U, Poly I:C (Johnson, 1994)
	Thalidomide derivatives	CC-4047/ACTIMID (J. Immunol., 168(10):4914-9)

Administration of a composition of the present invention to a host may be accomplished using any of a variety of techniques known to those of skill in the art. The composition(s) may be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals (i.e., a "pharmaceutical composition"). The pharmaceutical composition is preferably made in the form of a dosage unit containing a given amount of DNA, viral vector particles, polypeptide or peptide, for example. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The pharmaceutical composition may be administered orally, parentally, by inhalation spray, rectally, intranodally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term "pharmaceutically acceptable carrier" or "physiologically acceptable carrier" as used herein refers to one or more formulation materials suitable for accomplishing or enhancing the delivery of a nucleic acid, polypeptide, or peptide as a pharmaceutical composition. A "pharmaceutical composition" is a composition comprising a therapeutically effective amount of a nucleic acid or polypeptide. The terms "effective amount" and "therapeutically effective amount" each refer to the amount of a nucleic acid or polypeptide used to induce or enhance an effective immune response. It is preferred that compositions of the present invention provide for the induction or enhancement of an anti-tumor immune response in a host which protects the host from the development of a tumor and / or allows the host to eliminate an existing tumor from the body.

For oral administration, the pharmaceutical composition may be of any of several forms including, for example, a capsule, a tablet, a suspension, or liquid, among others. Liquids may be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrasternal, infusion, or intraperitoneal administration. Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature.

The dosage regimen for immunizing a host or otherwise treating a disorder or a disease with a composition of this invention is based on a variety of factors, including the type of disease, the age, weight, sex, medical condition of the patient, the severity of the condition, the route of administration, and the particular compound employed. For example, a poxviral vector may be administered as a composition comprising 1 x 10^6 infectious particles per dose. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods.

A prime-boost regimen may also be utilized (WO 01/30382 A1) in which the targeted immunogen is initially administered in a priming step in one form followed by a boosting step in which the targeted immunogen is administered in another form. The form of the targeted immunogen in the priming and boosting steps are different. For instance, if the priming step utilized a nucleic acid, the boost may be administered as a peptide. Similarly, where a priming step utilized one type of recombinant virus (i.e., ALVAC), the boost step may utilize another type of virus (i.e., NYVAC). This prime-boost method of administration has been shown to induce strong immunological responses. Various combinations of forms are suitable in practicing the present invention.

While the compositions of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other compositions or agents (i.e., other immunogenic targets, co-stimulatory molecules, adjuvants). When administered as a combination, the individual components can be formulated as separate compositions administered at the same time or different times, or the components can be combined as a single composition.

Injectable preparations, such as sterile injectable aqueous or oleaginous suspensions, may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Suitable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution, among others. For instance, a viral vector such as a poxvirus may be prepared in 0.4% NaCl. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

For topical administration, a suitable topical dose of a composition may be administered one to four, and preferably two or three times daily. The dose may also be administered with intervening days during which no does is applied. Suitable compositions may comprise from 0.001% to 10% w/w, for example, from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (*e.g.*, liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose.

The pharmaceutical compositions may also be prepared in a solid form (including granules, powders or suppositories). The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, *e.g.*, lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings. Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting sweetening, flavoring, and perfuming agents.

Pharmaceutical compositions comprising a nucleic acid or polypeptide of the present invention may take any of several forms and may be administered by any of several routes. In preferred embodiments, the compositions are administered via a parenteral route (intradermal, intramuscular or subcutaneous) to induce an immune response in the host. Alternatively, the composition may be administered directly into a lymph node (intranodal) or tumor mass (i.e., intratumoral administration). For example, the dose could be administered subcutaneously at days 0, 7, and 14. Suitable methods for immunization using compositions comprising TAs are known in the art, as shown for p53 (Hollstein et al., 1991), p21-ras (Almoguera et al., 1988), HER-2 (Fendly et al., 1990), the melanoma-associated antigens (MAGE-1; MAGE-2) (van der

Bruggen et al., 1991), p97 (Hu et al., 1988), melanoma-associated antigen E (WO 99/30737) and carcinoembryonic antigen (CEA) (Kantor et al., 1993; Fishbein et al., 1992; Kaufman et al., 1991), among others.

Preferred embodiments of administratable compositions include, for example, nucleic acids or polypeptides in liquid preparations such as suspensions, syrups, or elixirs. Preferred injectable preparations include, for example, nucleic acids or polypeptides suitable for parental, subcutaneous, intradermal, intramuscular or intravenous administration such as sterile suspensions or emulsions. For example, a recombinant poxvirus may be in admixture with a suitable carrier, diluent, or excipient such as sterile water, physiological saline, glucose or the like. The composition may also be provided in lyophilized form for reconstituting, for instance, in isotonic aqueous, saline buffer. In addition, the compositions can be co-administered or sequentially administered with other antineoplastic, anti-tumor or anti-cancer agents and/or with agents which reduce or alleviate ill effects of antineoplastic, anti-tumor or anti-cancer agents.

A kit comprising a composition of the present invention is also provided. The kit can include a separate container containing a suitable carrier, diluent or excipient. The kit can also include an additional anti-cancer, anti-tumor or antineoplastic agent and/or an agent that reduces or alleviates ill effects of antineoplastic, anti-tumor or anti-cancer agents for co- or sequential-administration. Additionally, the kit can include instructions for mixing or combining ingredients and/or administration.

A better understanding of the present invention and of its many advantages will be had from the following examples, given by way of illustration.

EXAMPLES

Example 1

Construction of the Multi-Antigen Construct vT416

The expression vector vT416 (ALVAC-NY-ESO-1/Trp-2-LFA-3/ICAM-1/B7.1-E3L/K3L) was constructed in the ALVAC vector using standard techniques. DNA sequences encoding NY-ESO-1, Trp-2, LFA-3, ICAM-1, B7.1, vvE3L and vvK3L were inserted into various loci within the ALVAC genome. DNA sequences encoding NY-ESO-1 (Chen et al. 1997 PNAS 94:1914) and TRP-2 (Wang et al. 1996 J. Exp. Med. 184:2207) were inserted into

the C5 locus. DNA sequences encoding LFA-3 (Wallner, et al. (1987) J. Exp. Med. 166:923-932), ICAM-1 (Staunton, et al. (1988) Cell 52:925-933) and B7.1 (Chen, et al. (1992) Cell 71:1093-1102) were inserted into the C3 locus. LFA-3, ICAM-1 and B7.1 form an expression cassette known as TRICOM. DNA sequences encoding vvE3L (Chang, et al. 1992. Proc. Natl. Acad. Sci. U. S. A 89:4825-4829) and vvK3L (Beattie, et al. 1991. Virology 183:419-422) were inserted into the C6 locus. Promoters were utilized as follows:

Table III

DNA sequence	Promoter
E3L	vaccinia E3L
K3L	vaccinia H6
LFA-3	vaccinia 30K
ICAM-1	vaccinia I3
B7.1	sE/L
NY-ESO-1	vaccinia H6
TRP-2	sE/L

Promoter sE/L is described by Chakrabarti, et al. (BioTechniques 23: 1094-1097, 1997).

The donor plasmids utilized are shown below:

Table IV

Plasmid	Size (bp)	Vector	Antibiotic Resitance Gene
pMPC6H6K3E3	-	pBS-SK	Amp
pALVAC.Tricom(C3) #33	10,470	pBS-SK	Amp
pT1132	11,154	pBS-SK	Amp

NY-ESO-1 and TRP-2 DNA sequences were inserted into the ALVAC donor plasmid pT1132. This donor plasmid was then used with pALVAC.Tricom(C3) #33 to generate the ALVAC-TRICOM recombinant expressing these genes using standard techniques. The plasmids pALVAC.Tricom(C3) #33 and pT1132 are shown in **Figure 1**. The DNA sequences of pALVAC.Tricom(C3) #33 and pT1132 are shown in **Figures 2 and 3**, respectively.

Example 2

Construction of the Multi-Antigen Construct vT419

The expression vector vT419 (ALVAC-gp100M/Mart-1/ Mage-1,3 minigene-LFA-3/ICAM-1/B7.1-E3L/K3L) was constructed in the ALVAC vector using standard techniques. DNA sequences encoding the gp100M/MART-1/MAGE-1,3 minigene, LFA-3, ICAM-1, B7.1, vvE3L and vvK3L were inserted into various loci within the ALVAC genome. The gp100M/ MART-1/MAGE-1,3 minigene was inserted into the C5 locus. DNA sequences encoding LFA-3 (Wallner, et al. (1987) J. Exp. Med. 166:923-932), ICAM-1 (Staunton, et al. (1988) Cell 52:925-933) and B7.1 (Chen, et al. (1992) Cell 71:1093-1102) were inserted into the C3 locus. LFA-3, ICAM-1 and B7.1 form an expression cassette known as TRICOM. DNA sequences encoding vvE3L (Chang, et al. 1992. Proc. Natl. Acad. Sci. U. S. A 89:4825-4829) and vvK3L (Beattie, et al. 1991. Virology 183:419-422) were inserted into the C6 locus. Promoters were utilized as follows:

Table V

Gene	Promoter
E3L	vaccinia E3L
K3L	vaccinia H6
LFA-3	vaccinia 30K
ICAM-1	vaccinia I3
B7.1	sE/L
gp100(M)	vaccinia H6
Mart-1	vaccinia 42K

Promoter sE/L is described by Chakrabarti, et al. (BioTechniques 23: 1094-1097, 1997).

The donor plasmids utilized are shown below:

Table VI

Plasmid	Size (bp)	Vector	Antibiotic Resitance Gene
PMPC6H6K3E3	-	pBS-SK	Amp
pALVAC.Tricom(C3) #33	10,470	pBS-SK	Amp
pT3217	11,465	pBS-SK	Amp

gp100(M), Mart-1 and Mage-1,3 minigene were inserted into the ALVAC C5 donor plasmid pT3217. This donor plasmid was then used with pALVAC.Tricom(C3) #33 to generate the ALVAC-TRICOM recombinant expressing these genes using standard techniques. This donor plasmid inserts into the C5 site. pALVAC.Tricom(C3) #33 is shown in **Figures 1** and **2.** The pT3217 plasmid is shown in **Figure 4**. The DNA sequence of pT3217 is shown in **Figure 5.**

EXAMPLE 3

Immunological Assessment of Multi-Antigen Vectors

The results of the first animal experiment indicated a trend toward higher immunological responses to three (Mart 1, NY-ESO-1 and gp100) of the four antigens when the vaccine was given as two separate injections. However, these differences were not statistically significant. In detail, HLA-A2/K^b transgenic mice (5/group) were immunized subcutaneously with vT419 (ALVAC(2)-gp100M/MART-1/MAGE-1/3 minigene/TRICOM) and vT416 (ALVAC(2)-TRP-2/NY-ESO-1/TRICOM) either combined at one site or given as separate injections. Control mice were immunized with parental ALVAC(2). Mice were vaccinated three times (at three week intervals), and three weeks after the last boost T cell responses in individual mice were analyzed by IFN-g ELISPOT and CTL assays following in vitro restimulation with peptide. Compared to control animals, mice vaccinated with the multi-antigen vectors (at 2 sites) exhibited statistically significant ELISPOT responses against MART-1. The IFN-gamma response to gp100M and NY-ESO-1 were also detectable, although these responses were not statistically significant due to response variability and the small number of cultures tested. ELISPOT responses against the TRP-2 antigen were elevated in all groups tested (including control animals), presumably due to the fact that the dominant A2-restricted TRP-2 peptide (180-188) cross-reacts with H-2K^b and can induce low avidity T cell responses in naïve mice following in vitro culture, and were therefore not statistically significant. Interestingly, ELISPOT responses in mice injected with an admixture of vT416 and vT419 were generally lower than in mice receiving each virus separately, although these differences did not achieve statistical significance. The CTL data were largely negative, except for one strong anti-gp100 response and one marginal anti-MART-1 response, both of which occurred in mice vaccinated with vT416 and vT419 (two sites). Overall, these results provided encouraging data that establish that the multi-antigen vectors can generate

responses against MART-1, and suggest that anti-gp100 and anti-NY-ESO-1 responses can also be induced.

Two additional pre-clinical animal studies have been completed using the melanoma multi-antigen ALVAC recombinants. In these experiments, HLA-A2/K^b transgenic mice (5/group) were immunized subcutaneously with vT419 (ALVAC(2)-gp100M/MART-1/MAGE-1/3 minigene/TRICOM) and vT416 (ALVAC(2)-TRP-2/NY-ESO-1/TRICOM) either combined at one site or given as separate injections. Control mice were immunized with parental ALVAC(2). After vaccination, the T cell responses in individual mice were assessed by IFN-gamma ELISPOT assay following in vitro restimulation with peptide. Unlike the previous multi-antigen experiment, which provided encouraging immunogenicity data, the two most recent studies generated inconclusive data, due to high background responses in control immunized animals. Therefore, overall the results were deemed as inconclusive.

To confirm the immunogenicity of the multi-antigen constructs, and to repeat results from the first study, another pre-clinical animal study has been completed. HLA-A2/K^b transgenic mice (10/group) were immunized subcutaneously with vT419 (ALVAC(2)-gp100M/MART-1/MAGE-1/3 minigene/TRICOM) and vT416 (ALVAC(2)-TRP-2/NY-ESO-1/TRICOM) given as separate injections. Control mice were immunized with parental ALVAC(2). Statistically significant ELISPOT responses were detectable against gp100, Mart-1 and TRP-2, and some responses were detected against NY-ESO-1, which were at the border of being statistically significant.

While the present invention has been described in terms of the preferred embodiments, it is understood that variations and modifications will occur to those skilled in the art. Therefore, it is intended that the appended claims cover all such equivalent variations that come within the scope of the invention as claimed.

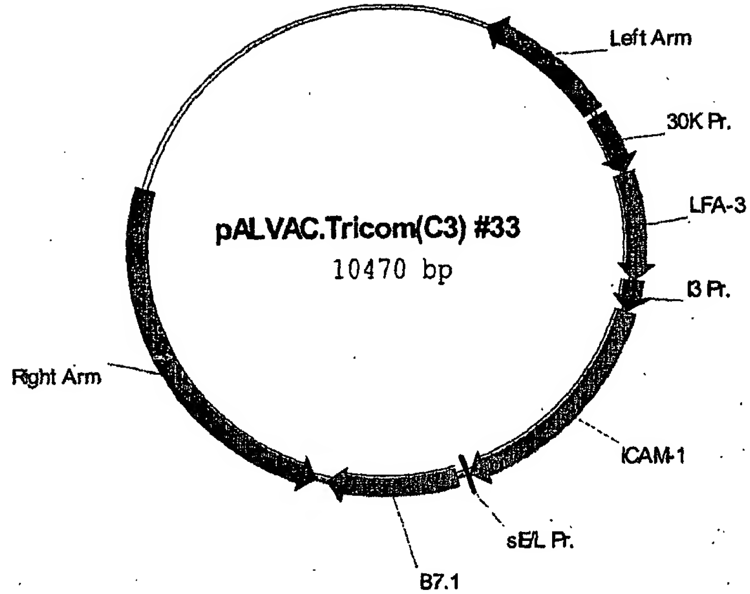
CLAIMS

What is claimed is:

1. An expression vector for co-expressing at least two immunogenic targets, wherein said immunogenic targets are selected from the group consisting of NY-ESO-1, TRP-2, gp100, gp100M, a MART antigen, MART-1, a MAGE antigen, MAGE-1, and MAGE-3.
2. The expression vector of claim 1 wherein the vector is a plasmid or a viral vector.
3. The expression vector of claim 2 wherein the viral vector is selected from the group consisting of poxvirus, adenovirus, retrovirus, herpesvirus, and adeno-associated virus.
4. The expression vector of claim 3 wherein the viral vector is a poxvirus selected from the group consisting of vaccinia, NYVAC, avipox, canarypox, ALVAC, ALVAC(2), fowlpox, and TROVAC.
5. The expression vector of claim 4 wherein the viral vector is a poxvirus selected from the group consisting of NYVAC, ALVAC, and ALVAC(2).
6. The expression vector of claim 1 further comprising at least one nucleic sequence encoding an angiogenesis-associated antigen.
7. The expression vector of claim 6 wherein the vector is a plasmid or a viral vector.
8. The expression vector of claim 7 wherein the viral vector is selected from the group consisting of poxvirus, adenovirus, retrovirus, herpesvirus, and adeno-associated virus.
9. The expression vector of claim 8 wherein the viral vector is a poxvirus selected from the group consisting of vaccinia, NYVAC, avipox, canarypox, ALVAC, ALVAC(2), fowlpox, and TROVAC.
10. The expression vector of claim 9 wherein the viral vector is a poxvirus selected from the group consisting of NYVAC, ALVAC, and ALVAC(2).
11. The expression vector of claim 1 or 6 further comprising at least one nucleic acid sequence encoding a co-stimulatory component.
12. The expression vector of claim 11 wherein the vector is a plasmid or a viral vector.
13. The expression vector of claim 12 wherein the viral vector is selected from the group consisting of poxvirus, adenovirus, retrovirus, herpesvirus, and adeno-associated virus.
14. The expression vector of claim 13 wherein the viral vector is a poxvirus selected from the group consisting of vaccinia, NYVAC, avipox, canarypox, ALVAC, ALVAC(2), fowlpox, and TROVAC.

15. The expression vector of claim 14 wherein the viral vector is a poxvirus selected from the group consisting of NYVAC, ALVAC, and ALVAC(2).
16. The expression vector of any one claims 11-15 wherein the co-stimulatory component is human B7.1.
17. A composition comprising an expression vector of any one of claims 1-16 in a pharmaceutically acceptable carrier.
18. A method for preventing or treating cancer comprising administering to a host an expression vector of any one of claims 1-16.
19. A method for preventing or treating cancer comprising administering to a host a composition of claim 17.

FIGURE 1


Left Arm
30K Pr.
LFA-3
I3 Pr.
ICAM-1
sE/L Pr.
B7.1
Right Arm
pALVAC.Tricom(C3) #33
10470 bp

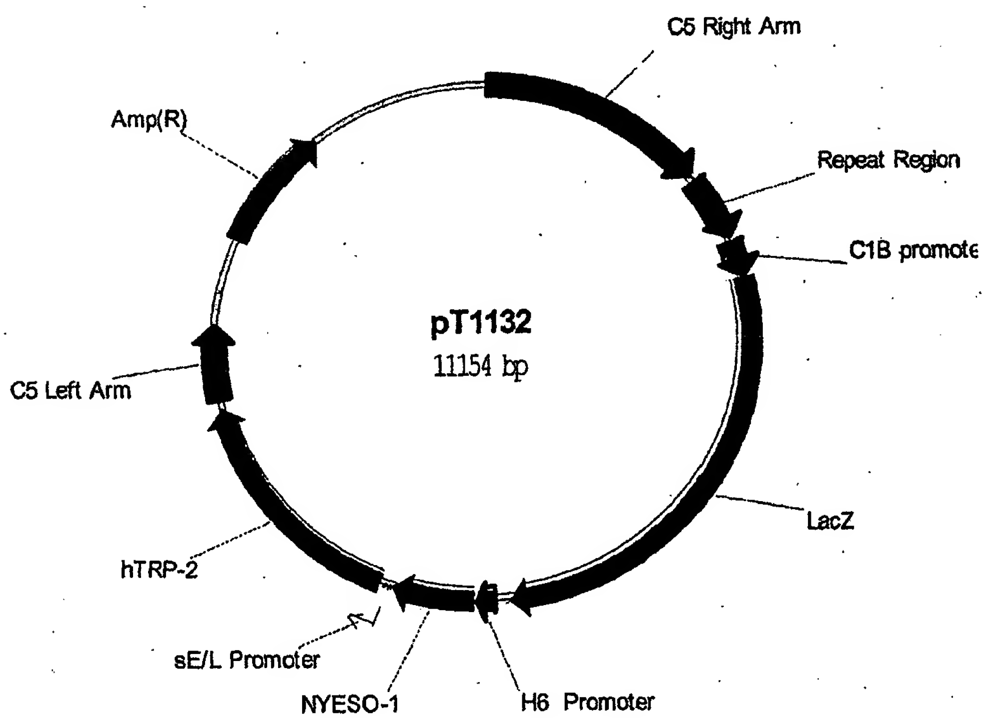

C5 Right Arm
Repeat Region
C1B promote
LacZ
H6 Promoter
NYESO-1
sE/L Promoter
hTRP-2
C5 Left Arm
Amp(R)
pT1132
11154 bp

FIGURE 2

DNA Sequence of pALVAC.Tricom(C3) #33

```
  1   GGAAATTGTA AACGTTAATA TTTTGTTAAA ATTCGCGTTA AATTTTTGTT
      CCTTTAACAT TTGCAATTAT AAAACAATTT TAAGCGCAAT TTAAAAACAA
 51   AAATCAGCTC ATTTTTTAAC CAATAGGCCG AAATCGGCAA AATCCCTTAT
      TTTAGTCGAG TAAAAAATTG GTTATCCGGC TTTAGCCGTT TTAGGGAATA
101   AAATCAAAAG AATAGACCGA GATAGGGTTG AGTGTTGTTC CAGTTTGGAA
      TTTAGTTTTC TTATCTGGCT CTATCCCAAC TCACAACAAG GTCAAACCTT
151   CAAGAGTCCA CTATTAAAGA ACGTGGACTC CAACGTCAAA GGGCGAAAAA
      GTTCTCAGGT GATAATTTCT TGCACCTGAG GTTGCAGTTT CCCGCTTTTT
201   CCGTCTATCA GGGCGATGGC CCACTACGTG AACCATCACC CTAATCAAGT
      GGCAGATAGT CCCGCTACCG GGTGATGCAC TTGGTAGTGG GATTAGTTCA
251   TTTTTGGGGT CGAGGTGCCG TAAAGCACTA AATCGGAACC CTAAAGGGAG
      AAAAACCCCA GCTCCACGGC ATTTCGTGAT TTAGCCTTGG GATTTCCCTC
301   CCCCCGATTT AGAGCTTGAC GGGGAAAGCC GGCGAACGTG GCGAGAAAGG
      GGGGGCTAAA TCTCGAACTG CCCCTTTCGG CCGCTTGCAC CGCTCTTTCC
351   AAGGGAAGAA AGCGAAAGGA GCGGGCGCTA GGGCGCTGGC AAGTGTAGCG
      TTCCCTTCTT TCGCTTTCCT CGCCCGCGAT CCCGCGACCG TTCACATCGC
401   GTCACGCTGC GCGTAACCAC CACACCCGCC GCGCTTAATG CGCCGCTACA
      CAGTGCGACG CGCATTGGTG GTGTGGGCGG CGCGAATTAC GCGGCGATGT
451   GGGCGCGTCG CGCCATTCGC CATTCAGGCT GCGCAACTGT TGGGAAGGGC
      CCCGCGCAGC GCGGTAAGCG GTAAGTCCGA CGCGTTGACA ACCCTTCCCG
501   GATCGGTGCG GGCCTCTTCG CTATTACGCC AGCTGGCGAA AGGGGGATGT
      CTAGCCACGC CCGGAGAAGC GATAATGCGG TCGACCGCTT TCCCCCTACA
551   GCTGCAAGGC GATTAAGTTG GGTAACGCCA GGGTTTTCCC AGTCACGACG
      CGACGTTCCG CTAATTCAAC CCATTGCGGT CCCAAAAGGG TCAGTGCTGC
601   TTGTAAAACG ACGGCCAGTG AATTGTAATA CGACTCACTA TAGGGCGAAT
      AACATTTTGC TGCCGGTCAC TTAACATTAT GCTGAGTGAT ATCCCGCTTA
651   TGGGTACCGC GGCCGCGTCG ACATGCATTG TTAGTTCTGT AGATCAGTAA
      ACCCATGGCG CCGGCGCAGC TGTACGTAAC AATCAAGACA TCTAGTCATT
                           ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                   Left Arm
701   CGTATAGCAT ACGAGTATAA TTATCGTAGG TAGTAGGTAT CCTAAAATAA
      GCATATCGTA TGCTCATATT AATAGCATCC ATCATCCATA GGATTTTATT
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                              Left Arm
751   ATCTGATACA GATAATAACT TTGTAAATCA ATTCAGCAAT TTCTCTATTA
      TAGACTATGT CTATTATTGA AACATTTAGT TAAGTCGTTA AAGAGATAAT
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                              Left Arm
801   TCATGATAAT GATTAATACA CAGCGTGTCG TTATTTTTTG TTACGATAGT
      AGTACTATTA CTAATTATGT GTCGCACAGC AATAAAAAAC AATGCTATCA
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                              Left Arm
851   ATTTCTAAAG TAAAGAGCAG GAATCCCTAG TATAATAGAA ATAATCCATA
      TAAAGATTTC ATTTCTCGTC CTTAGGGATC ATATTATCTT TATTAGGTAT
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                              Left Arm
901   TGAAAAATAT AGTAATGTAC ATATTTCTAA TGTTAACATA TTTATAGGTA
      ACTTTTTATA TCATTACATG TATAAAGATT ACAATTGTAT AAATATCCAT
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                              Left Arm
951   AATCCAGGAA GGGTAATTTT TACATATCTA TATACGCTTA TTACAGTTAT
      TTAGGTCCTT CCCATTAAAA ATGTATAGAT ATATGCGAAT AATGTCAATA
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                            Left Arm
1001   TAAAAATATA CTTGCAAACA TGTTAGAAGT AAAAAAGAAA GAACTAATTT
       ATTTTTATAT GAACGTTTGT ACAATCTTCA TTTTTTCTTT CTTGATTAAA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Left Arm
1051   TACAAAGTGC TTTACCAAAA TGCCAATGGA AATTACTTAG TATGTATATA
       ATGTTTCACG AAATGGTTTT ACGGTTACCT TTAATGAATC ATACATATAT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Left Arm
1101   ATGTATAAAG GTATGAATAT CACAAACAGC AAATCGGCTA TTCCCAAGTT
       TACATATTTC CATACTTATA GTGTTTGTCG TTTAGCCGAT AAGGGTTCAA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Left Arm

1151   GAGAAACGGT ATAATAGATA TATTTCTAGA TACCATTAAT AACCTTATAA
       CTCTTTGCCA TATTATCTAT ATAAAGATCT ATGGTAATTA TTGGAATATT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Left Arm
1201   GCTTGACGTT TCCTATAATG CCTACTAAGA AAACTAGAAG ATACATACAT
       CGAACTGCAA AGGATATTAC GGATGATTCT TTTGATCTTC TATGTATGTA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Left Arm
1251   ACTAACGCCA TACGAGAGTA ACTACTCATC GTATAACTAC TGTTGCTAAC
       TGATTGCGGT ATGCTCTCAT TGATGAGTAG CATATTGATG ACAACGATTG
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Left Arm
1301   AGTGACACTG ATGTTATAAC TCATCTTTGA TGTGGTATAA ATGTATAATA
       TCACTGTGAC TACAATATTG AGTAGAAACT ACACCATATT TACATATTAT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Left Arm
1351   ACTATATTAC ACTGGTATTT TATTTCAGTT ATATACTATA TAGTATTAAA
       TGATATAATG TGACCATAAA ATAAAGTCAA TATATGATAT ATCATAATTT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Left Arm
1401   AATTATATTT GTATAATTAT ATTATTATAT TCAGTGTAGA AAGTAAAATA
       TTAATATAAA CATATTAATA TAATAATATA AGTCACATCT TTCATTTTAT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Left Arm
1451   CTATAAATAT GTATCTCTTA TTTATAACTT ATTAGTAAAG TATGTACTAT
       GATATTTATA CATAGAGAAT AAATATTGAA TAATCATTTC ATACATGATA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Left Arm
1501   TCAGTTATAT TGTTTTATAA AAGCTAAATG CTACTAGATT GATATAAATG
       AGTCAATATA ACAAAATATT TTCGATTTAC GATGATCTAA CTATATTTAC
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Left Arm
1551   AATATGTAAT AAATTAGTAA TGTAGTATAC TAATATTAAC TCACATTTGA
       TTATACATTA TTTAATCATT ACATCATATG ATTATAATTG AGTGTAAACT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Left Arm
                                                      30K Pr.
                                                      ~~~~
1601   CTAATTAGCT ATAAAAACCC TAAGGTAGGC GGCCGCACTA GAGGATTCGA
       GATTAATCGA TATTTTTGGG ATTCCATCCG CCGGCGTGAT CTCCTAAGCT
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                   30K Pr.
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1651 CAAACACCAA TAATTCCCTT CTCTTCATTC CGGACATTAA ATTGGCTATA
     GTTTGTGGTT ATTAAGGGAA GAGAAGTAAG GCCTGTAATT TAACCGATAT
                   30K Pr.
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1701 GATAATAAAG ACATTGAGAT GTTACAGGCT CTGTTCAAAT ACGACATTAA
     CTATTATTTC TGTAACTCTA CAATGTCCGA GACAAGTTTA TGCTGTAATT
                   30K Pr.
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1751 TATCTATTCT GCTAATCTGG AAAATGTACT ATTGGATGAT GCCGAAATAG
     ATAGATAAGA CGATTAGACC TTTTACATGA TAACCTACTA CGGCTTTATC
                   30K Pr.
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1801 CTAAAATGAT TATAGAAAAG CATGTTGAAT ACAAGTCTGA CTCCTATACA
     GATTTTACTA ATATCTTTTC GTACAACTTA TGTTCAGACT GAGGATATGT
                   30K Pr.
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1851 AAAGATCTCG ATATAGTCAA GAATAATAAA TTGGATGAAA TAATTAGCAA
     TTTCTAGAGC TATATCAGTT CTTATTATTT AACCTACTTT ATTAATCGTT
                   30K Pr.
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1901 AAACAAGGAA CTCAGACTCA TGTACGTCAA TTGTGTAAAG AAAAACTAAT
     TTTGTTCCTT GAGTCTGAGT ACATGCAGTT AACACATTTC TTTTTGATTA
                   30K Pr.
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1951 TAGATTCTCC CACATTTTTG TTAACATTAC ACTAACTAAT TGGTAAAATT
     ATCTAAGAGG GTGTAAAAAC AATTGTAATG TGATTGATTA ACCATTTTAA
                   30K Pr.
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2001 GATAGAATAA TTATGTGTAT ATAAGATAGA TTTCCTATTG TCTTACTCAT
     CTATCTTATT AATACACATA TATTCTATCT AAAGGATAAC AGAATGAGTA
               30K Pr.
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                                                hLFA-3
                                          ~~~~~~~~~~~~~~~~~~
2051 TGCATCGTGG GAATTCAGAT CAGCTTCCGC GGCATGGTTG CTGGGAGCGA
     ACGTAGCACC CTTAAGTCTA GTCGAAGGCG CCGTACCAAC GACCCTCGCT
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                       hLFA-3
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2101  CGCGGGGCGG GCCCTGGGGG TCCTCAGCGT GGTCTGCCTG CTGCACTGCT
      GCGCCCCGCC CGGGACCCCC AGGAGTCGCA CCAGACGGAC GACGTGACGA
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2151  TTGGTTTCAT CAGCTGTTTT TCCCAACAAA TATATGGTGT TGTGTATGGG
      AACCAAAGTA GTCGACAAAA AGGGTTGTTT ATATACCACA ACACATACCC
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2201  AATGTAACTT TCCATGTACC AAGCAATGTG CCTTTAAAAG AGGTCCTATG
      TTACATTGAA AGGTACATGG TTCGTTACAC GGAAATTTTC TCCAGGATAC
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2251  GAAAAAACAA AAGGATAAAG TTGCAGAACT GGAAAATTCT GAATTCAGAG
      CTTTTTTGTT TTCCTATTTC AACGTCTTGA CCTTTTAAGA CTTAAGTCTC
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2301  CTTTCTCATC TTTTAAAAAT AGGGTTTATT TAGACACTGT GTCAGGTAGC
      GAAAGAGTAG AAAATTTTTA TCCCAAATAA ATCTGTGACA CAGTCCATCG
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2351  CTCACTATCT ACAACTTAAC ATCATCAGAT GAAGATGAGT ATGAAATGGA
      GAGTGATAGA TGTTGAATTG TAGTAGTCTA CTTCTACTCA TACTTTACCT
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2401  ATCGCCAAAT ATTACTGATA CCATGAAGTT CTTTCTTTAT GTGCTTGAGT
      TAGCGGTTTA TAATGACTAT GGTACTTCAA GAAAGAAATA CACGAACTCA
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2451  CTCTTCCATC TCCCACACTA ACTTGTGCAT TGACTAATGG AAGCATTGAA
      GAGAAGGTAG AGGGTGTGAT TGAACACGTA ACTGATTACC TTCGTAACTT
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2501  GTCCAATGCA TGATACCAGA GCATTACAAC AGCCATCGAG GACTTATAAT
      CAGGTTACGT ACTATGGTCT CGTAATGTTG TCGGTAGCTC CTGAATATTA
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2551  GTACTCATGG GATTGTCCTA TGGAGCAATG TAAACGTAAC TCAACCAGTA
      CATGAGTACC CTAACAGGAT ACCTCGTTAC ATTTGCATTG AGTTGGTCAT
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2601  TATATTTTAA GATGGAAAAT GATCTTCCAC AAAAAATACA GTGTACTCTT
      ATATAAAATT CTACCTTTTA CTAGAAGGTG TTTTTTATGT CACATGAGAA
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2651  AGCAATCCAT TATTTAATAC AACATCATCA ATCATTTTGA CAACCTGTAT
      TCGTTAGGTA ATAAATTATG TTGTAGTAGT TAGTAAAACT GTTGGACATA
                       hLFA-3
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2701  CCCAAGCAGC GGTCATTCAA GACACAGATA TGCACTTATA CCCATACCAT
      GGGTTCGTCG CCAGTAAGTT CTGTGTCTAT ACGTGAATAT GGGTATGGTA
                       hLFA-3
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2751  TAGCAGTAAT TACAACATGT ATTGTGCTGT ATATGAATGG TATTCTGAAA
      ATCGTCATTA ATGTTGTACA TAACACGACA TATACTTACC ATAAGACTTT
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                 hLFA-3                                    I3 Pr.
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2801     TGTGACAGAA AACCAGACAG AACCAACTCC AATTGATTGG CTCGACCGGG
         ACACTGTCTT TTGGTCTGTC TTGGTTGAGG TTAACTAACC GAGCTGGCCC
                                 I3 Pr.
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2851     AATGTACTAT CTACGTACGA AACCCGCATC CGCTCCCATT CAATTCACAT
         TTACATGATA GATGCATGCT TTGGGCGTAG GCGAGGGTAA GTTAAGTGTA
                                 I3 Pr.
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2901     TGGACAAGGA TAAAATAAAA CCACTGGTGG TTTGCGATTC CGAAATCTGT
         ACCTGTTCCT ATTTTATTTT GGTGACCACC AAACGCTAAG GCTTTAGACA
                                 I3 Pr.
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2951     ACATCATGCA GTGGTTAAAC AAAAACATTT TTATTCTCAA ATGAGATAAA
         TGTAGTACGT CACCAATTTG TTTTTGTAAA AATAAGAGTT TACTCTATTT
                                 I3 Pr.
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3001     GTGAAAATAT ATATCATTAT ATTACAAAGT ACAATTATTT AGGTTTAATC
         CACTTTTATA TATAGTAATA TAATGTTTCA TGTTAATAAA TCCAAATTAG
           I3 Pr.                            hICAM
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3051     AATCCCGCGG GCTATGGCTC CCAGCAGCCC CCGGCCCGCG CTGCCCGCAC
         TTAGGGCGCC CGATACCGAG GGTCGTCGGG GGCCGGGCGC GACGGGCGTG
                                 hICAM
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3101     TCCTGGTCCT GCTCGGGGCT CTGTTCCCAG GACCTGGCAA TGCCCAGACA
         AGGACCAGGA CGAGCCCCGA GACAAGGGTC CTGGACCGTT ACGGGTCTGT
                                 hICAM
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3151     TCTGTGTCCC CCTCAAAAGT CATCCTGCCC CGGGGAGGCT CCGTGCTGGT
         AGACACAGGG GGAGTTTTCA GTAGGACGGG GCCCCTCCGA GGCACGACCA
                                 hICAM
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3201     GACATGCAGC ACCTCCTGTG ACCAGCCCAA GTTGTTGGGC ATAGAGACCC
         CTGTACGTCG TGGAGGACAC TGGTCGGGTT CAACAACCCG TATCTCTGGG
                                 hICAM
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3251     CGTTGCCTAA AAAGGAGTTG CTCCTGCCTG GGAACAACCG GAAGGTGTAT
         GCAACGGATT TTTCCTCAAC GAGGACGGAC CCTTGTTGGC CTTCCACATA
                                 hICAM
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3301     GAACTGAGCA ATGTGCAAGA AGATAGCCAA CCAATGTGCT ATTCAAACTG
         CTTGACTCGT TACACGTTCT TCTATCGGTT GGTTACACGA TAAGTTTGAC
                                 hICAM
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3351     CCCTGATGGG CAGTCAACAG CTAAAACCTT CCTCACCGTG TACTGGACTC
         GGGACTACCC GTCAGTTGTC GATTTTGGAA GGAGTGGCAC ATGACCTGAG
                                 hICAM
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3401     CAGAACGGGT GGAACTGGCA CCCCTCCCCT CTTGGCAGCC AGTGGGCAAG
         GTCTTGCCCA CCTTGACCGT GGGGAGGGGA GAACCGTCGG TCACCCGTTC
                                 hICAM
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3451     AACCTTACCC TACGCTGCCA GGTGGAGGGT GGGGCACCCC GGGCCAACCT
         TTGGAATGGG ATGCGACGGT CCACCTCCCA CCCCGTGGGG CCCGGTTGGA
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                                  hICAM
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3501    CACCGTGGTG CTGCTCCGTG GGGAGAAGGA GCTGAAACGG GAGCCAGCTG
        GTGGCACCAC GACGAGGCAC CCCTCTTCCT CGACTTTGCC CTCGGTCGAC
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3551    TGGGGGAGCC CGCTGAGGTC ACGACCACGG TGCTGGTGAG GAGAGATCAC
        ACCCCCTCGG GCGACTCCAG TGCTGGTGCC ACGACCACTC CTCTCTAGTG
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3601    CATGGAGCCA ATTTCTCGTG CCGCACTGAA CTGGACCTGC GGCCCCAAGG
        GTACCTCGGT TAAAGAGCAC GGCGTGACTT GACCTGGACG CCGGGGTTCC
                                  hICAM
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3651    GCTGGAGCTG TTTGAGAACA CCTCGGCCCC CTACCAGCTC CAGACCTTTG
        CGACCTCGAC AAACTCTTGT GGAGCCGGGG GATGGTCGAG GTCTGGAAAC
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3701    TCCTGCCAGC GACTCCCCCA CAACTTGTCA GCCCCCGGGT CCTAGAGGTG
        AGGACGGTCG CTGAGGGGGT GTTGAACAGT CGGGGGCCCA GGATCTCCAC
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3751    GACACGCAGG GGACCGTGGT CTGTTCCCTG GACGGGCTGT TCCCAGTCTC
        CTGTGCGTCC CCTGGCACCA GACAAGGGAC CTGCCCGACA AGGGTCAGAG
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3801    GGAGGCCCAG GTCCACCTGG CACTGGGGGA CCAGAGGTTG AACCCCACAG
        CCTCCGGGTC CAGGTGGACC GTGACCCCCT GGTCTCCAAC TTGGGGTGTC
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3851    TCACCTATGG CAACGACTCC TTCTCGGCCA AGGCCTCAGT CAGTGTGACC
        AGTGGATACC GTTGCTGAGG AAGAGCCGGT TCCGGAGTCA GTCACACTGG
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3901    GCAGAGGACG AGGGCACCCA GCGGCTGACG TGTGCAGTAA TACTGGGGAA
        CGTCTCCTGC TCCCGTGGGT CGCCGACTGC ACACGTCATT ATGACCCCTT
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3951    CCAGAGCCAG GAGACACTGC AGACAGTGAC CATCTACAGC TTTCCGGCGC
        GGTCTCGGTC CTCTGTGACG TCTGTCACTG GTAGATGTCG AAAGGCCGCG
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4001    CCAACGTGAT TCTGACGAAG CCAGAGGTCT CAGAAGGGAC CGAGGTGACA
        GGTTGCACTA AGACTGCTTC GGTCTCCAGA GTCTTCCCTG GCTCCACTGT
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4051    GTGAAGTGTG AGGCCCACCC TAGAGCCAAG GTGACGCTGA ATGGGGTTCC
        CACTTCACAC TCCGGGTGGG ATCTCGGTTC CACTGCGACT TACCCCAAGG
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4101    AGCCCAGCCA CTGGGCCCGA GGGCCCAGCT CCTGCTGAAG GCCACCCCAG
        TCGGGTCGGT GACCCGGGCT CCCGGGTCGA GGACGACTTC CGGTGGGGTC
                                  hICAM
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4151    AGGACAACGG GCGCAGCTTC TCCTGCTCTG CAACCCTGGA GGTGGCCGGC
        TCCTGTTGCC CGCGTCGAAG AGGACGAGAC GTTGGGACCT CCACCGGCCG
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                         hICAM
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4201  CAGCTTATAC ACAAGAACCA GACCCGGGAG CTTCGTGTCC TGTATGGCCC
      GTCGAATATG TGTTCTTGGT CTGGGCCCTC GAAGCACAGG ACATACCGGG
                         hICAM
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4251  CCGACTGGAC GAGAGGGATT GTCCGGGAAA CTGGACGTGG CCAGAAAATT
      GGCTGACCTG CTCTCCCTAA CAGGCCCTTT GACCTGCACC GGTCTTTTAA
                         hICAM
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4301  CCCAGCAGAC TCCAATGTGC CAGGCTTGGG GGAACCCATT GCCCGAGCTC
      GGGTCGTCTG AGGTTACACG GTCCGAACCC CCTTGGGTAA CGGGCTCGAG
                         hICAM
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4351  AAGTGTCTAA AGGATGGCAC TTTCCCACTG CCCATCGGGG AATCAGTGAC
      TTCACAGATT TCCTACCGTG AAAGGGTGAC GGGTAGCCCC TTAGTCACTG
                         hICAM
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4401  TGTCACTCGA GATCTTGAGG GCACCTACCT CTGTCGGGCC AGGAGCACTC
      ACAGTGAGCT CTAGAACTCC CGTGGATGGA GACAGCCCGG TCCTCGTGAG
                         hICAM
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4451  AAGGGGAGGT CACCCGCGAG GTGACCGTGA ATGTGCTCTC CCCCCGGTAT
      TTCCCCTCCA GTGGGCGCTC CACTGGCACT TACACGAGAG GGGGGCCATA
                         hICAM
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4501  GAGATTGTCA TCATCACTGT GGTAGCAGCC GCAGTCATAA TGGGCACTGC
      CTCTAACAGT AGTAGTGACA CCATCGTCGG CGTCAGTATT ACCCGTGACG
                         hICAM
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4551  AGGCCTCAGC ACGTACCTCT ATAACCGCCA GCGGAAGATC AAGAAATACA
      TCCGGAGTCG TGCATGGAGA TATTGGCGGT CGCCTTCTAG TTCTTTATGT
                         hICAM
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4601  GACTACAACA GGCCCAAAAA GGGACCCCCA TGAAACCGAA CACACAAGCC
      CTGATGTTGT CCGGGTTTTT CCCTGGGGGT ACTTTGGCTT GTGTGTTCGG
        hICAM                                sE/L Pr.
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4651  ACGCCTCCCT GAGCATGCAT GTAGCTTAAA AATTGAAATT TTATTTTTTT
      TGCGGAGGGA CTCGTACGTA CATCGAATTT TTAACTTTAA AATAAAAAAA
         sE/L Pr.
      ~~~~~~~~~~~~~~~~~
4701  TTTTTGGAAT ATAAATAAGC TCGAAGTCGA AATTCCTGCA GCCCGGGGCC
      AAAAACCTTA TATTTATTCG AGCTTCAGCT TTAAGGACGT CGGGCCCCGG
                         hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4751  ATGGGCCACA CACGGAGGCA GGGAACATCA CCATCCAAGT GTCCATACCT
      TACCCGGTGT GTGCCTCCGT CCCTTGTAGT GGTAGGTTCA CAGGTATGGA
                         hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4801  CAATTTCTTT CAGCTCTTGG TGCTGGCTGG TCTTTCTCAC TTCTGTTCAG
      GTTAAAGAAA GTCGAGAACC ACGACCGACC AGAAAGAGTG AAGACAAGTC
                         hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4851  GTGTTATCCA CGTGACCAAG GAAGTGAAAG AAGTGGCAAC GCTGTCCTGT
      CACAATAGGT GCACTGGTTC CTTCACTTTC TTCACCGTTG CGACAGGACA
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                          hB7.1
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4901  GGTCACAATG TTTCTGTTGA AGAGCTGGCA CAAACTCGCA TCTACTGGCA
      CCAGTGTTAC AAAGACAACT TCTCGACCGT GTTTGAGCGT AGATGACCGT
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4951  AAAGGAGAAG AAAATGGTGC TGACTATGAT GTCTGGAGAC ATGAATATAT
      TTTCCTCTTC TTTTACCACG ACTGATACTA CAGACCTCTG TACTTATATA
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5001  GGCCCGAGTA CAAGAACCGG ACCATCTTTG ATATCACTAA TAACCTCTCC
      CCGGGCTCAT GTTCTTGGCC TGGTAGAAAC TATAGTGATT ATTGGAGAGG
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5051  ATTGTGATCC TGGCTCTGCG CCCATCTGAC GAGGGCACAT ACGAGTGTGT
      TAACACTAGG ACCGAGACGC GGGTAGACTG CTCCCGTGTA TGCTCACACA
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5101  TGTTCTGAAG TATGAAAAAG ACGCTTTCAA GCGGGAACAC CTGGCTGAAG
      ACAAGACTTC ATACTTTTTC TGCGAAAGTT CGCCCTTGTG GACCGACTTC
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5151  TGACGTTATC AGTCAAAGCT GACTTCCCTA CACCTAGTAT ATCTGACTTT
      ACTGCAATAG TCAGTTTCGA CTGAAGGGAT GTGGATCATA TAGACTGAAA
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5201  GAAATTCCAA CTTCTAATAT TAGAAGGATA ATTTGCTCAA CCTCTGGAGG
      CTTTAAGGTT GAAGATTATA ATCTTCCTAT TAAACGAGTT GGAGACCTCC
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5251  TTTTCCAGAG CCTCACCTCT CCTGGTTGGA AAATGGAGAA GAATTAAATG
      AAAAGGTCTC GGAGTGGAGA GGACCAACCT TTTACCTCTT CTTAATTTAC
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5301  CCATCAACAC AACAGTTTCC CAAGATCCTG AAACTGAGCT CTATGCTGTT
      GGTAGTTGTG TTGTCAAAGG GTTCTAGGAC TTTGACTCGA GATACGACAA
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5351  AGCAGCAAAC TGGATTTCAA TATGACAACC AACCACAGCT TCATGTGTCT
      TCGTCGTTTG ACCTAAAGTT ATACTGTTGG TTGGTGTCGA AGTACACAGA
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5401  CATCAAGTAT GGACATTTAA GAGTGAATCA GACCTTCAAC TGGAATACAA
      GTAGTTCATA CCTGTAAATT CTCACTTAGT CTGGAAGTTG ACCTTATGTT
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5451  CCAAGCAAGA GCATTTTCCT GATAACCTGC TCCCATCCTG GGCCATTACC
      GGTTCGTTCT CGTAAAAGGA CTATTGGACG AGGGTAGGAC CCGGTAATGG
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5501  TTAATCTCAG TAAATGGAAT TTTCGTGATA TGCTGCCTGA CCTACTGCTT
      AATTAGAGTC ATTTACCTTA AAAGCACTAT ACGACGGACT GGATGACGAA
                          hB7.1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5551  TGCCCCACGC TGCAGAGAGA GAAGGAGGAA TGAGAGATTG AGAAGGGAAA
      ACGGGGTGCG ACGTCTCTCT CTTCCTCCTT ACTCTCTAAC TCTTCCCTTT
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            hB7.1
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5601   GTGTACGCCC TGTATAAAAG CTTTCTAGGT TTTTGTTTAG GGCTGCAGGA
       CACATGCGGG ACATATTTTC GAAAGATCCA AAAACAAATC CCGACGTCCT
5651   ATTCCTCGAG GGATCCCGAT TTTTATGACT AGTTAATCAA ATAAAAAGCA
       TAAGGAGCTC CCTAGGGCTA AAAATACTGA TCAATTAGTT TATTTTTCGT
                                                    Right Arm
5701   TACAAGCTAT TGCTTCGCTA TCGTTACAAA ATGGCAGGAA TTTTGTGTAA
       ATGTTCGATA ACGAAGCGAT AGCAATGTTT TACCGTCCTT AAAACACATT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
5751   ACTAAGCCAC ATACTTGCCA ATGAAAAAAA TAGTAGAAAG GATACTATTT
       TGATTCGGTG TATGAACGGT TACTTTTTTT ATCATCTTTC CTATGATAAA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
5801   TAATGGGATT AGATGTTAAG GTTCCTTGGG ATTATAGTAA CTGGGCATCT
       ATTACCCTAA TCTACAATTC CAAGGAACCC TAATATCATT GACCCGTAGA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
5851   GTTAACTTTT ACGACGTTAG GTTAGATACT GATGTTACAG ATTATAATAA
       CAATTGAAAA TGCTGCAATC CAATCTATGA CTACAATGTC TAATATTATT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
5901   TGTTACAATA AAATACATGA CAGGATGTGA TATTTTTCCT CATATAACTC
       ACAATGTTAT TTTATGTACT GTCCTACACT ATAAAAAGGA GTATATTGAG
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
5951   TTGGAATAGC AAATATGGAT CAATGTGATA GATTTGAAAA TTTCAAAAAG
       AACCTTATCG TTTATACCTA GTTACACTAT CTAAACTTTT AAAGTTTTTC
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
6001   CAAATAACTG ATCAAGATTT ACAGACTATT TCTATAGTCT GTAAAGAAGA
       GTTTATTGAC TAGTTCTAAA TGTCTGATAA AGATATCAGA CATTTCTTCT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
6051   GATGTGTTTT CCTCAGAGTA ACGCCTCTAA ACAGTTGGGA GCGAAAGGAT
       CTACACAAAA GGAGTCTCAT TGCGGAGATT TGTCAACCCT CGCTTTCCTA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
6101   GCGCTGTAGT TATGAAACTG GAGGTATCTG ATGAACTTAG AGCCCTAAGA
       CGCGACATCA ATACTTTGAC CTCCATAGAC TACTTGAATC TCGGGATTCT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
6151   AATGTTCTGC TGAATGCGGT ACCCTGTTCG AAGGACGTGT TTGGTGATAT
       TTACAAGACG ACTTACGCCA TGGGACAAGC TTCCTGCACA AACCACTATA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
6201   CACAGTAGAT AATCCGTGGA ATCCTCACAT AACAGTAGGA TATGTTAAGG
       GTGTCATCTA TTAGGCACCT TAGGAGTGTA TTGTCATCCT ATACAATTCC
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
6251   AGGACGATGT CGAAAACAAG AAACGCCTAA TGGAGTGCAT GTCCAAGTTT
       TCCTGCTACA GCTTTTGTTC TTTGCGGATT ACCTCACGTA CAGGTTCAAA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                          Right Arm
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6301   AGGGGGCAAG AAATACAAGT TCTAGGATGG TATTAATAAG TATCTAAGTA
       TCCCCCGTTC TTTATGTTCA AGATCCTACC ATAATTATTC ATAGATTCAT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6351   TTTGGTATAA TTTATTAAAT AGTATAATTA TAACAAATAA TAAATAACAT
       AAACCATATT AAATAATTTA TCATATTAAT ATTGTTTATT ATTTATTGTA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6401   GATAACGGTT TTTATTAGAA TAAAATAGAG ATAATATCAT AATGATATAT
       CTATTGCCAA AAATAATCTT ATTTTATCTC TATTATAGTA TTACTATATA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6451   AATACTTCAT TACCAGAAAT GAGTAATGGA AGACTTATAA ATGAACTGCA
       TTATGAAGTA ATGGTCTTTA CTCATTACCT TCTGAATATT TACTTGACGT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6501   TAAAGCTATA AGGTATAGAG ATATAAATTT AGTAAGGTAT ATACTTAAAA
       ATTTCGATAT TCCATATCTC TATATTTAAA TCATTCCATA TATGAATTTT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6551   AATGCAAATA CAATAACGTA AATATACTAT CAACGTCTTT GTATTTAGCC
       TTACGTTTAT GTTATTGCAT TTATATGATA GTTGCAGAAA CATAAATCGG
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6601   GTAAGTATTT CTGATATAGA AATGGTAAAA TTATTACTAG AACACGGTGC
       CATTCATAAA GACTATATCT TTACCATTTT AATAATGATC TTGTGCCACG
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6651   CGATATTTTA AAATGTAAAA ATCCTCCTCT TCATAAAGCT GCTAGTTTAG
       GCTATAAAAT TTTACATTTT TAGGAGGAGA AGTATTTCGA CGATCAAATC
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6701   ATAATACAGA AATTGCTAAA CTACTAATAG ATTCTGGCGC TGACATAGAA
       TATTATGTCT TTAACGATTT GATGATTATC TAAGACCGCG ACTGTATCTT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6751   CAGATACATT CTGGAAATAG TCCGTTATAT ATTTCTGTAT ATAGAAACAA
       GTCTATGTAA GACCTTTATC AGGCAATATA TAAAGACATA TATCTTTGTT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6801   TAAGTCATTA ACTAGATATT TATTAAAAAA AGGTGTTAAT TGTAATAGAT
       ATTCAGTAAT TGATCTATAA ATAATTTTTT TCCACAATTA ACATTATCTA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6851   TCTTTCTAAA TTATTACGAT GTACTGTATG ATAAGATATC TGATGATATG
       AGAAAGATTT AATAATGCTA CATGACATAC TATTCTATAG ACTACTATAC
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6901   TATAAAATAT TTATAGATTT TAATATTGAT CTTAATATAC AAACTAGAAA
       ATATTTTATA AATATCTAAA ATTATAACTA GAATTATATG TTTGATCTTT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
6951   TTTTGAAACT CCGTTACATT ACGCTATAAA GTATAAGAAT ATAGATTTAA
       AAAACTTTGA GGCAATGTAA TGCGATATTT CATATTCTTA TATCTAAATT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                            Right Arm
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7001   TTAGGATATT GTTAGATAAT AGTATTAAAA TAGATAAAAG TTTATTTTTG
       AATCCTATAA CAATCTATTA TCATAATTTT ATCTATTTTC AAATAAAAAC
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7051   CATAAACAGT ATCTCATAAA GGCACTTAAA AATAATTGTA GTTACGATAT
       GTATTTGTCA TAGAGTATTT CCGTGAATTT TTATTAACAT CAATGCTATA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7101   AATAGCGTTA CTTATAAATC ACGGAGTGCC TATAAACGAA CAAGATGATT
       TTATCGCAAT GAATATTTAG TGCCTCACGG ATATTTGCTT GTTCTACTAA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7151   TAGGTAAAAC CCCATTACAT CATTCGGTAA TTAATAGAAG AAAAGATGTA
       ATCCATTTTG GGGTAATGTA GTAAGCCATT AATTATCTTC TTTTCTACAT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7201   ACAGCACTTC TGTTAAATCT AGGAGCTGAT ATAAACGTAA TAGATGACTG
       TGTCGTGAAG ACAATTTAGA TCCTCGACTA TATTTGCATT ATCTACTGAC
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7251   TATGGGCAGT CCCTTACATT ACGCTGTTTC ACGTAACGAT ATCGAAACAA
       ATACCCGTCA GGGAATGTAA TGCGACAAAG TGCATTGCTA TAGCTTTGTT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7301   CAAAGACACT TTTAGAAAGA GGATCTAATG TTAATGTGGT TAATAATCAT
       GTTTCTGTGA AAATCTTTCT CCTAGATTAC AATTACACCA ATTATTAGTA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7351   ATAGATACCG TTCTAAATAT AGCTGTTGCA TCTAAAAACA AAACTATAGT
       TATCTATGGC AAGATTTATA TCGACAACGT AGATTTTTGT TTTGATATCA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7401   AAACTTATTA CTGAAGTACG GTACTGATAC AAAGTTGGTA GGATTAGATA
       TTTGAATAAT GACTTCATGC CATGACTATG TTTCAACCAT CCTAATCTAT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7451   AACATGTTAT TCACATAGCT ATAGAAATGA AAGATATTAA TATACTGAAT
       TTGTACAATA AGTGTATCGA TATCTTTACT TTCTATAATT ATATGACTTA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7501   GCGATCTTAT TATATGGTTG CTATGTAAAC GTCTATAATC ATAAAGGTTT
       CGCTAGAATA ATATACCAAC GATACATTTG CAGATATTAG TATTTCCAAA
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7551   CACTCCTCTA TACATGGCAG TTAGTTCTAT GAAAACAGAA TTTGTTAAAC
       GTGAGGAGAT ATGTACCGTC AATCAAGATA CTTTTGTCTT AAACAATTTG
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7601   TCTTACTTGA CCACGGTGCT TACGTAAATG CTAAAGCTAA GTTATCTGGA
       AGAATGAACT GGTGCCACGA ATGCATTTAC GATTTCGATT CAATAGACCT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                             Right Arm
7651   AATACTCCTT TACATAAAGC TATGTTATCT AATAGTTTTA ATAATATAAA
       TTATGAGGAA ATGTATTTCG ATACAATAGA TTATCAAAAT TATTATATTT
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
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                         Right Arm
7701  ATTACTTTTA TCTTATAACG CCGACTATAA TTCTCTAAAT AATCACGGTA
      TAATGAAAAT AGAATATTGC GGCTGATATT AAGAGATTTA TTAGTGCCAT
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                         Right Arm
7751  ATACGCCTCT AACTTGTGTT AGCTTTTTAG ATGACAAGAT AGCTATTATG
      TATGCGGAGA TTGAACACAA TCGAAAAATC TACTGTTCTA TCGATAATAC
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                         Right Arm
7801  ATAATATCTA AAATGATGTT AGAAATATCT AAAAATCCTG AAATAGCTAA
      TATTATAGAT TTTACTACAA TCTTTATAGA TTTTTAGGAC TTTATCGATT
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                         Right Arm
7851  TTCAGAAGGT TTTATAGTAA ACATGGAACA TATAAACAGT AATAAAAGAC
      AAGTCTTCCA AAATATCATT TGTACCTTGT ATATTTGTCA TTATTTTCTG
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                         Right Arm
7901  TACTATCTAT AAAAGAATCA TGCGAAAAAG AACTAGATGT TATAACACAT
      ATGATAGATA TTTTCTTAGT ACGCTTTTTC TTGATCTACA ATATTGTGTA
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                         Right Arm
7951  ATAAAGTTAA ATTCTATATA TTCTTTTAAT ATCTTTCTTG ACAATAACAT
      TATTTCAATT TAAGATATAT AAGAAAATTA TAGAAAGAAC TGTTATTGTA
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                         Right Arm
8001  AGATCTTATG GTAAAGTTCG TAACTAATCC TAGAGTTAAT AAGATACCTG
      TCTAGAATAC CATTTCAAGC ATTGATTAGG ATCTCAATTA TTCTATGGAC
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                         Right Arm
8051  CATGTATACG TATATATAGG GAATTAATAC GGAAAAATAA ATCATTAGCT
      GTACATATGC ATATATATCC CTTAATTATG CCTTTTTATT TAGTAATCGA
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                         Right Arm
8101  TTTCATAGAC ATCAGCTAAT AGTTAAAGCT GTAAAAGAGA GTAAGAATCT
      AAAGTATCTG TAGTCGATTA TCAATTTCGA CATTTTCTCT CATTCTTAGA
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                         Right Arm
8151  AGGAATAATA GGTAGGTTAC CTATAGATAT CAAACATATA ATAATGGAAC
      TCCTTATTAT CCATCCAATG GATATCTATA GTTTGTATAT TATTACCTTG
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                         Right Arm
8201  TATTAAGTAA TAATGATTTA CATTCTGTTA TCACCAGCTG TTGTAACCCA
      ATAATTCATT ATTACTAAAT GTAAGACAAT AGTGGTCGAC AACATTGGGT
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                         Right Arm
8251  GTAGTATAAA GAGCTCCAGC TTTTGTTCCC TTTAGTGAGG GTTAATTCCG
      CATCATATTT CTCGAGGTCG AAAACAAGGG AAATCACTCC CAATTAAGGC
      ~~~~~~~~~~~~~~~~~~
        Right Arm
8301  AGCTTGGCGT AATCATGGTC ATAGCTGTTT CCTGTGTGAA ATTGTTATCC
      TCGAACCGCA TTAGTACCAG TATCGACAAA GGACACACTT TAACAATAGG
8351  GCTCACAATT CCACACAACA TACGAGCCGG AAGCATAAAG TGTAAAGCCT
      CGAGTGTTAA GGTGTGTTGT ATGCTCGGCC TTCGTATTTC ACATTTCGGA
8401  GGGGTGCCTA ATGAGTGAGC TAACTCACAT TAATTGCGTT GCGCTCACTG
      CCCCACGGAT TACTCACTCG ATTGAGTGTA ATTAACGCAA CGCGAGTGAC
8451  CCCGCTTTCC AGTCGGGAAA CCTGTCGTGC CAGCTGCATT AATGAATCGG
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      GGGCGAAAGG TCAGCCCTTT GGACAGCACG GTCGACGTAA TTACTTAGCC
8501  CCAACGCGCG GGGAGAGGCG GTTTGCGTAT TGGGCGCTCT TCCGCTTCCT
      GGTTGCGCGC CCCTCTCCGC CAAACGCATA ACCCGCGAGA AGGCGAAGGA
8551  CGCTCACTGA CTCGCTGCGC TCGGTCGTTC GGCTGCGGCG AGCGGTATCA
      GCGAGTGACT GAGCGACGCG AGCCAGCAAG CCGACGCCGC TCGCCATAGT
8601  GCTCACTCAA AGGCGGTAAT ACGGTTATCC ACAGAATCAG GGGATAACGC
      CGAGTGAGTT TCCGCCATTA TGCCAATAGG TGTCTTAGTC CCCTATTGCG
8651  AGGAAAGAAC ATGTGAGCAA AAGGCCAGCA AAAGGCCAGG AACCGTAAAA
      TCCTTTCTTG TACACTCGTT TTCCGGTCGT TTTCCGGTCC TTGGCATTTT
8701  AGGCCGCGTT GCTGGCGTTT TTCCATAGGC TCCGCCCCCC TGACGAGCAT
      TCCGGCGCAA CGACCGCAAA AAGGTATCCG AGGCGGGGGG ACTGCTCGTA
8751  CACAAAAATC GACGCTCAAG TCAGAGGTGG CGAAACCCGA CAGGACTATA
      GTGTTTTTAG CTGCGAGTTC AGTCTCCACC GCTTTGGGCT GTCCTGATAT
8801  AAGATACCAG GCGTTTCCCC CTGGAAGCTC CCTCGTGCGC TCTCCTGTTC
      TTCTATGGTC CGCAAAGGGG GACCTTCGAG GGAGCACGCG AGAGGACAAG
8851  CGACCCTGCC GCTTACCGGA TACCTGTCCG CCTTTCTCCC TTCGGGAAGC
      GCTGGGACGG CGAATGGCCT ATGGACAGGC GGAAAGAGGG AAGCCCTTCG
8901  GTGGCGCTTT CTCATAGCTC ACGCTGTAGG TATCTCAGTT CGGTGTAGGT
      CACCGCGAAA GAGTATCGAG TGCGACATCC ATAGAGTCAA GCCACATCCA
8951  CGTTCGCTCC AAGCTGGGCT GTGTGCACGA ACCCCCCGTT CAGCCCGACC
      GCAAGCGAGG TTCGACCCGA CACACGTGCT TGGGGGGCAA GTCGGGCTGG
9001  GCTGCGCCTT ATCCGGTAAC TATCGTCTTG AGTCCAACCC GGTAAGACAC
      CGACGCGGAA TAGGCCATTG ATAGCAGAAC TCAGGTTGGG CCATTCTGTG
9051  GACTTATCGC CACTGGCAGC AGCCACTGGT AACAGGATTA GCAGAGCGAG
      CTGAATAGCG GTGACCGTCG TCGGTGACCA TTGTCCTAAT CGTCTCGCTC
9101  GTATGTAGGC GGTGCTACAG AGTTCTTGAA GTGGTGGCCT AACTACGGCT
      CATACATCCG CCACGATGTC TCAAGAACTT CACCACCGGA TTGATGCCGA
9151  ACACTAGAAG GACAGTATTT GGTATCTGCG CTCTGCTGAA GCCAGTTACC
      TGTGATCTTC CTGTCATAAA CCATAGACGC GAGACGACTT CGGTCAATGG
9201  TTCGGAAAAA GAGTTGGTAG CTCTTGATCC GGCAAACAAA CCACCGCTGG
      AAGCCTTTTT CTCAACCATC GAGAACTAGG CCGTTTGTTT GGTGGCGACC
9251  TAGCGGTGGT TTTTTTGTTT GCAAGCAGCA GATTACGCGC AGAAAAAAAG
      ATCGCCACCA AAAAAACAAA CGTTCGTCGT CTAATGCGCG TCTTTTTTTC
9301  GATCTCAAGA AGATCCTTTG ATCTTTTCTA CGGGGTCTGA CGCTCAGTGG
      CTAGAGTTCT TCTAGGAAAC TAGAAAAGAT GCCCCAGACT GCGAGTCACC
9351  AACGAAAACT CACGTTAAGG GATTTTGGTC ATGAGATTAT CAAAAAGGAT
      TTGCTTTTGA GTGCAATTCC CTAAAACCAG TACTCTAATA GTTTTTCCTA
9401  CTTCACCTAG ATCCTTTTAA ATTAAAAATG AAGTTTTAAA TCAATCTAAA
      GAAGTGGATC TAGGAAAATT TAATTTTTAC TTCAAAATTT AGTTAGATTT
9451  GTATATATGA GTAAACTTGG TCTGACAGTT ACCAATGCTT AATCAGTGAG
      CATATATACT CATTTGAACC AGACTGTCAA TGGTTACGAA TTAGTCACTC
9501  GCACCTATCT CAGCGATCTG TCTATTTCGT TCATCCATAG TTGCCTGACT
      CGTGGATAGA GTCGCTAGAC AGATAAAGCA AGTAGGTATC AACGGACTGA
9551  CCCCGTCGTG TAGATAACTA CGATACGGGA GGGCTTACCA TCTGGCCCCA
      GGGGCAGCAC ATCTATTGAT GCTATGCCCT CCCGAATGGT AGACCGGGGT
9601  GTGCTGCAAT GATACCGCGA GACCCACGCT CACCGGCTCC AGATTTATCA
      CACGACGTTA CTATGGCGCT CTGGGTGCGA GTGGCCGAGG TCTAAATAGT
9651  GCAATAAACC AGCCAGCCGG AAGGGCCGAG CGCAGAAGTG GTCCTGCAAC
      CGTTATTTGG TCGGTCGGCC TTCCCGGCTC GCGTCTTCAC CAGGACGTTG
9701  TTTATCCGCC TCCATCCAGT CTATTAATTG TTGCCGGGAA GCTAGAGTAA
      AAATAGGCGG AGGTAGGTCA GATAATTAAC AACGGCCCTT CGATCTCATT
9751  GTAGTTCGCC AGTTAATAGT TTGCGCAACG TTGTTGCCAT TGCTACAGGC
      CATCAAGCGG TCAATTATCA AACGCGTTGC AACAACGGTA ACGATGTCCG
9801  ATCGTGGTGT CACGCTCGTC GTTTGGTATG GCTTCATTCA GCTCCGGTTC
      TAGCACCACA GTGCGAGCAG CAAACCATAC CGAAGTAAGT CGAGGCCAAG
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9851   CCAACGATCA AGGCGAGTTA CATGATCCCC CATGTTGTGC AAAAAAGCGG
       GGTTGCTAGT TCCGCTCAAT GTACTAGGGG GTACAACACG TTTTTTCGCC
9901   TTAGCTCCTT CGGTCCTCCG ATCGTTGTCA GAAGTAAGTT GGCCGCAGTG
       AATCGAGGAA GCCAGGAGGC TAGCAACAGT CTTCATTCAA CCGGCGTCAC
9951   TTATCACTCA TGGTTATGGC AGCACTGCAT AATTCTCTTA CTGTCATGCC
       AATAGTGAGT ACCAATACCG TCGTGACGTA TTAAGAGAAT GACAGTACGG
10001  ATCCGTAAGA TGCTTTTCTG TGACTGGTGA GTACTCAACC AAGTCATTCT
       TAGGCATTCT ACGAAAAGAC ACTGACCACT CATGAGTTGG TTCAGTAAGA
10051  GAGAATAGTG TATGCGGCGA CCGAGTTGCT CTTGCCCGGC GTCAATACGG
       CTCTTATCAC ATACGCCGCT GGCTCAACGA GAACGGGCCG CAGTTATGCC
10101  GATAATACCG CGCCACATAG CAGAACTTTA AAAGTGCTCA TCATTGGAAA
       CTATTATGGC GCGGTGTATC GTCTTGAAAT TTTCACGAGT AGTAACCTTT
10151  ACGTTCTTCG GGGCGAAAAC TCTCAAGGAT CTTACCGCTG TTGAGATCCA
       TGCAAGAAGC CCCGCTTTTG AGAGTTCCTA GAATGGCGAC AACTCTAGGT
10201  GTTCGATGTA ACCCACTCGT GCACCCAACT GATCTTCAGC ATCTTTTACT
       CAAGCTACAT TGGGTGAGCA CGTGGGTTGA CTAGAAGTCG TAGAAAATGA
10251  TTCACCAGCG TTTCTGGGTG AGCAAAAACA GGAAGGCAAA ATGCCGCAAA
       AAGTGGTCGC AAAGACCCAC TCGTTTTTGT CCTTCCGTTT TACGGCGTTT
10301  AAAGGGAATA AGGGCGACAC GGAAATGTTG AATACTCATA CTCTTCCTTT
       TTTCCCTTAT TCCCGCTGTG CCTTTACAAC TTATGAGTAT GAGAAGGAAA
10351  TTCAATATTA TTGAAGCATT TATCAGGGTT ATTGTCTCAT GAGCGGATAC
       AAGTTATAAT AACTTCGTAA ATAGTCCCAA TAACAGAGTA CTCGCCTATG
10401  ATATTTGAAT GTATTTAGAA AAATAAACAA ATAGGGGTTC CGCGCACATT
       TATAAACTTA CATAAATCTT TTTATTTGTT TATCCCCAAG GCGCGTGTAA
10451  TCCCCGAAAA GTGCCACCTG AGGGGCTTTT CACGGTGGAC
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FIGURE 3: Donor plasmid p1132

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                        C5 Right Arm
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  1    TGAATGTTAA ATGTTATACT TTGGATGAAG CTATAAATAT GCATTGGAAA
       ACTTACAATT TACAATATGA AACCTACTTC GATATTTATA CGTAACCTTT
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 51    AATAATCCAT TTAAAGAAAG GATTCAAATA CTACAAAACC TAAGCGATAA
       TTATTAGGTA AATTTCTTTC CTAAGTTTAT GATGTTTTGG ATTCGCTATT
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
101    TATGTTAACT AAGCTTATTC TTAACGACGC TTTAAATATA CACAAATAAA
       ATACAATTGA TTCGAATAAG AATTGCTGCG AAATTTATAT GTGTTTATTT
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
151    CATAATTTTT GTATAACCTA ACAAATAACT AAAACATAAA AATAATAAAA
       GTATTAAAAA CATATTGGAT TGTTTATTGA TTTTGTATTT TTATTATTTT
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
201    GGAAATGTAA TATCGTAATT ATTTTACTCA GGAATGGGGT TAAATATTTA
       CCTTTACATT ATAGCATTAA TAAAATGAGT CCTTACCCCA ATTTATAAAT
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
251    TATCACGTGT ATATCTATAC TGTTATCGTA TACTCTTTAC AATTACTATT
       ATAGTGCACA TATAGATATG ACAATAGCAT ATGAGAAATG TTAATGATAA
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
301    ACGAATATGC AAGAGATAAT AAGATTACGT ATTTAAGAGA ATCTTGTCAT
       TGCTTATACG TTCTCTATTA TTCTAATGCA TAAATTCTCT TAGAACAGTA
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
351    GATAATTGGG TACGACATAG TGATAAATGC TATTTCGCAT CGTTACATAA
       CTATTAACCC ATGCTGTATC ACTATTTACG ATAAAGCGTA GCAATGTATT
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
401    AGTCAGTTGG AAAGATGGAT TTGACAGATG TAACTTAATA GGTGCAAAAA
       TCAGTCAACC TTTCTACCTA AACTGTCTAC ATTGAATTAT CCACGTTTTT
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
451    TGTTAAATAA CAGCATTCTA TCGGAAGATA GGATACCAGT TATATTATAC
       ACAATTTATT GTCGTAAGAT AGCCTTCTAT CCTATGGTCA ATATAATATG
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
501    AAAAATCACT GGTTGGATAA AACAGATTCT GCAATATTCG TAAAAGATGA
       TTTTTAGTGA CCAACCTATT TTGTCTAAGA CGTTATAAGC ATTTTCTACT
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
551    AGATTACTGC GAATTTGTAA ACTATGACAA TAAAAAGCCA TTTATCTCAA
       TCTAATGACG CTTAAACATT TGATACTGTT ATTTTTCGGT AAATAGAGTT
                        C5 Right Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
601    CGACATCGTG TAATTCTTCC ATGTTTTATG TATGTGTTTC AGATATTATG
       GCTGTAGCAC ATTAAGAAGG TACAAAATAC ATACACAAAG TCTATAATAC
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                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     651  AGATTACTAT AAACTTTTTG TATACTTATA TTCCGTAAAC TATATTAATC
          TCTAATGATA TTTGAAAAAC ATATGAATAT AAGGCATTTG ATATAATTAG
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     701  ATGAAGAAAA TGAAAAAGTA TAGAAGCTGT TCACGAGCGG TTGTTGAAAA
          TACTTCTTTT ACTTTTTCAT ATCTTCGACA AGTGCTCGCC AACAACTTTT
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     751  CAACAAAATT ATACATTCAA GATGGCTTAC ATATACGTCT GTGAGGCTAT
          GTTGTTTTAA TATGTAAGTT CTACCGAATG TATATGCAGA CACTCCGATA
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     801  CATGGATAAT GACAATGCAT CTCTAAATAG GTTTTTGGAC AATGGATTCG
          GTACCTATTA CTGTTACGTA GAGATTTATC CAAAAACCTG TTACCTAAGC
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     851  ACCCTAACAC GGAATATGGT ACTCTACAAT CTCCTCTTGA AATGGCTGTA
          TGGGATTGTG CCTTATACCA TGAGATGTTA GAGGAGAACT TTACCGACAT
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     901  ATGTTCAAGA ATACCGAGGC TATAAAAATC TTGATGAGGT ATGGAGCTAA
          TACAAGTTCT TATGGCTCCG ATATTTTTAG AACTACTCCA TACCTCGATT
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     951  ACCTGTAGTT ACTGAATGCA CAACTTCTTG TCTGCATGAT GCGGTGTTGA
          TGGACATCAA TGACTTACGT GTTGAAGAAC AGACGTACTA CGCCACAACT
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    1001  GAGACGACTA CAAAATAGTG AAAGATCTGT TGAAGAATAA CTATGTAAAC
          CTCTGCTGAT GTTTTATCAC TTTCTAGACA ACTTCTTATT GATACATTTG
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    1051  AATGTTCTTT ACAGCGGAGG CTTTACTCCT TTGTGTTTGG CAGCTTACCT
          TTACAAGAAA TGTCGCCTCC GAAATGAGGA AACACAAACC GTCGAATGGA
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    1101  TAACAAAGTT AATTTGGTTA AACTTCTATT GGCTCATTCG GCGGATGTAG
          ATTGTTTCAA TTAAACCAAT TTGAAGATAA CCGAGTAAGC CGCCTACATC
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    1151  ATATTTCAAA CACGGATCGG TTAACTCCTC TACATATAGC CGTATCAAAT
          TATAAAGTTT GTGCCTAGCC AATTGAGGAG ATGTATATCG GCATAGTTTA
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    1201  AAAAATTTAA CAATGGTTAA ACTTCTATTG AACAAAGGTG CTGATACTGA
          TTTTTAAATT GTTACCAATT TGAAGATAAC TTGTTTCCAC GACTATGACT
                              C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    1251  CTTGCTGGAT AACATGGGAT GTACTCCTTT AATGATCGCT GTACAATCTG
          GAACGACCTA TTGTACCCTA CATGAGGAAA TTACTAGCGA CATGTTAGAC
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                         C5 Right Arm
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1301     GAAATATTGA AATATGTAGC ACACTACTTA AAAAAAATAA AATGTCCAGA
         CTTTATAACT TTATACATCG TGTGATGAAT TTTTTTTATT TTACAGGTCT
                         C5 Right Arm
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1351     ACTGGGAAAA ATTGATCTTG CCAGCTGTAA TTCATGGTAG AAAAGAAGTG
         TGACCCTTTT TAACTAGAAC GGTCGACATT AAGTACCATC TTTTCTTCAC
                         C5 Right Arm
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1401     CTCAGGCTAC TTTTCAACAA AGGAGCAGAT GTAAACTACA TCTTTGAAAG
         GAGTCCGATG AAAAGTTGTT TCCTCGTCTA CATTTGATGT AGAAACTTTC
                         C5 Right Arm
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1451     AAATGGAAAA TCATATACTG TTTTGGAATT GATTAAAGAA AGTTACTCTG
         TTTACCTTTT AGTATATGAC AAAACCTTAA CTAATTTCTT TCAATGAGAC
                 C5 Right Arm
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1501     AGACACAAAA GAGGTAGCTG AAGTGGTACT CTCAAAGGTA CGTGACTAAT
         TCTGTGTTTT CTCCATCGAC TTCACCATGA GAGTTTCCAT GCACTGATTA
                                                 Repeat Region
                                                 ~~~~~~~~~~
1551     TAGCTATAAA AAGGATCGGC CGCTCTAGAA CTAGTGGATC GGGTTCTTTA
         ATCGATATTT TTCCTAGCCG GCGAGATCTT GATCACCTAG CCCAAGAAAT
                        Repeat Region
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1601     TTCTATACTT AAAAAGTGAA AATAAATACA AAGGTTCTTG AGGGTTGTGT
         AAGATATGAA TTTTTCACTT TTATTTATGT TTCCAAGAAC TCCCAACACA
                        Repeat Region
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1651     TAAATTGAAA GCGAGAAATA ATCATAAATT ATTTCATTAT CGCGATATCC
         ATTTAACTTT CGCTCTTTAT TAGTATTTAA TAAAGTAATA GCGCTATAGG
                        Repeat Region
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1701     GTTAAGTTTG TATCGTACCC CGATCCCCCG AGCCATGCAG GCCGAAGGCC
         CAATTCAAAC ATAGCATGGG GCTAGGGGGC TCGGTACGTC CGGCTTCCGG
                        Repeat Region
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1751     GGGGCACAGG GGGTTCGACG GGCGATGCTG ATGGCCCAGG AGGCCCTGGC
         CCCCGTGTCC CCCAAGCTGC CCGCTACGAC TACCGGGTCC TCCGGGACCG
                        Repeat Region
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1801     ATTCCTGATG GCCCAGGGGG CAATGCTGGC GGCCCAGGAG AGGCGGGTGC
         TAAGGACTAC CGGGTCCCCC GTTACGACCG CCGGGTCCTC TCCGCCCACG
                        Repeat Region
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1851     CACGGGCGGC AGAGGTCCCC GGGGCGCAGG GGCAGCAAGG GCCTCGGGGC
         GTGCCCGCCG TCTCCAGGGG CCCCGCGTCC CCGTCGTTCC CGGAGCCCCG
                        Repeat Region
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1901     CGGGAGGAGG CGCCCCGCGG GGTCCGCATG GCGGCGCGGC TTCAGGGCTG
         GCCCTCCTCC GCGGGGCGCC CCAGGCGTAC CGCCGCGCCG AAGTCCCGAC
                        Repeat Region
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1951     AATGGATGCT GCAGATGCGG GGCCAGGGGG CCGGAGAGCC GCCTGCTTGA
         TTACCTACGA CGTCTACGCC CCGGTCCCCC GGCCTCTCGG CGGACGAACT
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               Repeat Region
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2001 GTTCTACCTC GCCATGCCTT TCGCGACACC CATAGCTTGA TATCGAATTC
     CAAGATGGAG CGGTACGGAA AGCGCTGTGG GTATCGAACT ATAGCTTAAG
                                         C1B promoter
                                    ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2051 TAGGGGGATC CACTAGTTCT AGAGGATCAT TATTTAACGT AAACTAAATG
     ATCCCCCTAG GTGATCAAGA TCTCCTAGTA ATAAATTGCA TTTGATTTAC
                           C1B promoter
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2101 GAAAAGCTAT TTACAGGTAC ATACGGTGTT TTTCTGGAAT CAAATGATTC
     CTTTTCGATA AATGTCCATG TATGCCACAA AAAGACCTTA GTTTACTAAG
                           C1B promoter
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2151 TGATTTTGAG GATTTTATCA ATACAATAAT GACAGTGCTA ACTGGTAAAA
     ACTAAAACTC CTAAAATAGT TATGTTATTA CTGTCACGAT TGACCATTTT
                           C1B promoter
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2201 AAGAAAGCAA ACAATTATCA TGGCTAACAA TTTTTATTAT ATTTGTAGTA
     TTCTTTCGTT TGTTAATAGT ACCGATTGTT AAAAATAATA TAAACATCAT
                           C1B promoter
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2251 TGCATAGTGG TCTTTACGTT TCTTTATTTA AAGTTAATGT GTTAAGATTA
     ACGTATCACC AGAAATGCAA AGAAATAAAT TTCAATTACA CAATTCTAAT
       C1B promoter                           LacZ
     ~~~~~~~~~~~~~~~~~~           ~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2301 AATGGAGTAA TTGGATCCCC CATCGATGGG GAATTCACTG GCCGTCGTTT
     TTACCTCATT AACCTAGGGG GTAGCTACCC CTTAAGTGAC CGGCAGCAAA
                               LacZ
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2351 TACAACGTCG TGACTGGGAA AACCCTGGCG TTACCCAACT TAATCGCCTT
     ATGTTGCAGC ACTGACCCTT TTGGGACCGC AATGGGTTGA ATTAGCGGAA
                               LacZ
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2401 GCAGCACATC CCCCTTTCGC CAGCTGGCGT AATAGCGAAG AGGCCCGCAC
     CGTCGTGTAG GGGGAAAGCG GTCGACCGCA TTATCGCTTC TCCGGGCGTG
                               LacZ
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2451 CGATCGCCCT TCCCAACAGT TGCGCAGCCT GAATGGCGAA TGGCGCTTTG
     GCTAGCGGGA AGGGTTGTCA ACGCGTCGGA CTTACCGCTT ACCGCGAAAC
                               LacZ
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2501 CCTGGTTTCC GGCACCAGAA GCGGTGCCGG AAAGCTGGCT GGAGTGCGAT
     GGACCAAAGG CCGTGGTCTT CGCCACGGCC TTTCGACCGA CCTCACGCTA
                               LacZ
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2551 CTTCCTGAGG CCGATACTGT CGTCGTCCCC TCAAACTGGC AGATGCACGG
     GAAGGACTCC GGCTATGACA GCAGCAGGGG AGTTTGACCG TCTACGTGCC
                               LacZ
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2601 TTACGATGCG CCCATCTACA CCAACGTGAC CTATCCCATT ACGGTCAATC
     AATGCTACGC GGGTAGATGT GGTTGCACTG GATAGGGTAA TGCCAGTTAG
                               LacZ
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2651 CGCCGTTTGT TCCCACGGAG AATCCGACGG GTTGTTACTC GCTCACATTT
     GCGGCAAACA AGGGTGCCTC TTAGGCTGCC CAACAATGAG CGAGTGTAAA
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                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  2701    AATGTTGATG AAAGCTGGCT ACAGGAAGGC CAGACGCGAA TTATTTTTGA
          TTACAACTAC TTTCGACCGA TGTCCTTCCG GTCTGCGCTT AATAAAAACT
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  2751    TGGCGTTAAC TCGGCGTTTC ATCTGTGGTG CAACGGGCGC TGGGTCGGTT
          ACCGCAATTG AGCCGCAAAG TAGACACCAC GTTGCCCGCG ACCCAGCCAA
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  2801    ACGGCCAGGA CAGTCGTTTG CCGTCTGAAT TTGACCTGAG CGCATTTTTA
          TGCCGGTCCT GTCAGCAAAC GGCAGACTTA AACTGGACTC GCGTAAAAAT
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  2851    CGCGCCGGAG AAAACCGCCT CGCGGTGATG GTGCTGCGCT GGAGTGACGG
          GCGCGGCCTC TTTTGGCGGA GCGCCACTAC CACGACGCGA CCTCACTGCC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  2901    CAGTTATCTG GAAGATCAGG ATATGTGGCG GATGAGCGGC ATTTTCCGTG
          GTCAATAGAC CTTCTAGTCC TATACACCGC CTACTCGCCG TAAAAGGCAC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  2951    ACGTCTCGTT GCTGCATAAA CCGACTACAC AAATCAGCGA TTTCCATGTT
          TGCAGAGCAA CGACGTATTT GGCTGATGTG TTTAGTCGCT AAAGGTACAA
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  3001    GCCACTCGCT TTAATGATGA TTTCAGCCGC GCTGTACTGG AGGCTGAAGT
          CGGTGAGCGA AATTACTACT AAAGTCGGCG CGACATGACC TCCGACTTCA
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  3051    TCAGATGTGC GGCGAGTTGC GTGACTACCT ACGGGTAACA GTTTCTTTAT
          AGTCTACACG CCGCTCAACG CACTGATGGA TGCCCATTGT CAAAGAAATA
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  3101    GGCAGGGTGA AACGCAGGTC GCCAGCGGCA CCGCGCCTTT CGGCGGTGAA
          CCGTCCCACT TTGCGTCCAG CGGTCGCCGT GGCGCGGAAA GCCGCCACTT
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  3151    ATTATCGATG AGCGTGGTGG TTATGCCGAT CGCGTCACAC TACGTCTGAA
          TAATAGCTAC TCGCACCACC AATACGGCTA GCGCAGTGTG ATGCAGACTT
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  3201    CGTCGAAAAC CCGAAACTGT GGAGCGCCGA AATCCCGAAT CTCTATCGTG
          GCAGCTTTTG GGCTTTGACA CCTCGCGGCT TTAGGGCTTA GAGATAGCAC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  3251    CGGTGGTTGA ACTGCACACC GCCGACGGCA CGCTGATTGA AGCAGAAGCC
          GCCACCAACT TGACGTGTGG CGGCTGCCGT GCGACTAACT TCGTCTTCGG
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  3301    TGCGATGTCG GTTTCCGCGA GGTGCGGATT GAAAATGGTC TGCTGCTGCT
          ACGCTACAGC CAAAGGCGCT CCACGCCTAA CTTTTACCAG ACGACGACGA
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  3351    GAACGGCAAG CCGTTGCTGA TTCGAGGCGT TAACCGTCAC GAGCATCATC
          CTTGCCGTTC GGCAACGACT AAGCTCCGCA ATTGGCAGTG CTCGTAGTAG
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                                 LacZ
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    3401  CTCTGCATGG TCAGGTCATG GATGAGCAGA CGATGGTGCA GGATATCCTG
          GAGACGTACC AGTCCAGTAC CTACTCGTCT GCTACCACGT CCTATAGGAC
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    3451  CTGATGAAGC AGAACAACTT TAACGCCGTG CGCTGTTCGC ATTATCCGAA
          GACTACTTCG TCTTGTTGAA ATTGCGGCAC GCGACAAGCG TAATAGGCTT
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    3501  CCATCCGCTG TGGTACACGC TGTGCGACCG CTACGGCCTG TATGTGGTGG
          GGTAGGCGAC ACCATGTGCG ACACGCTGGC GATGCCGGAC ATACACCACC
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    3551  ATGAAGCCAA TATTGAAACC CACGGCATGG TGCCAATGAA TCGTCTGACC
          TACTTCGGTT ATAACTTTGG GTGCCGTACC ACGGTTACTT AGCAGACTGG
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    3601  GATGATCCGC GCTGGCTACC GGCGATGAGC GAACGCGTAA CGCGAATGGT
          CTACTAGGCG CGACCGATGG CCGCTACTCG CTTGCGCATT GCGCTTACCA
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    3651  GCAGCGCGAT CGTAATCACC CGAGTGTGAT CATCTGGTCG CTGGGGAATG
          CGTCGCGCTA GCATTAGTGG GCTCACACTA GTAGACCAGC GACCCCTTAC
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    3701  AATCAGGCCA CGGCGCTAAT CACGACGCGC TGTATCGCTG GATCAAATCT
          TTAGTCCGGT GCCGCGATTA GTGCTGCGCG ACATAGCGAC CTAGTTTAGA
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    3751  GTCGATCCTT CCCGCCCGGT GCAGTATGAA GGCGGCGGAG CCGACACCAC
          CAGCTAGGAA GGGCGGGCCA CGTCATACTT CCGCCGCCTC GGCTGTGGTG
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    3801  GGCCACCGAT ATTATTTGCC CGATGTACGC GCGCGTGGAT GAAGACCAGC
          CCGGTGGCTA TAATAAACGG GCTACATGCG CGCGCACCTA CTTCTGGTCG
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    3851  CCTTCCCGGC TGTGCCGAAA TGGTCCATCA AAAAATGGCT TTCGCTACCT
          GGAAGGGCCG ACACGGCTTT ACCAGGTAGT TTTTTACCGA AAGCGATGGA
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    3901  GGAGAGACGC GCCCGCTGAT CCTTTGCGAA TACGCCCACG CGATGGGTAA
          CCTCTCTGCG CGGGCGACTA GGAAACGCTT ATGCGGGTGC GCTACCCATT
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    3951  CAGTCTTGGC GGTTTCGCTA AATACTGGCA GGCGTTTCGT CAGTATCCCC
          GTCAGAACCG CCAAAGCGAT TTATGACCGT CCGCAAAGCA GTCATAGGGG
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4001  GTTTACAGGG CGGCTTCGTC TGGGACTGGG TGGATCAGTC GCTGATTAAA
          CAAATGTCCC GCCGAAGCAG ACCCTGACCC ACCTAGTCAG CGACTAATTT
                                 LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4051  TATGATGAAA ACGGCAACCC GTGGTCGGCT TACGGCGGTG ATTTTGGCGA
          ATACTACTTT TGCCGTTGGG CACCAGCCGA ATGCCGCCAC TAAAACCGCT
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                              LacZ
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4101    TACGCCGAAC GATCGCCAGT TCTGTATGAA CGGTCTGGTC TTTGCCGACC
        ATGCGGCTTG CTAGCGGTCA AGACATACTT GCCAGACCAG AAACGGCTGG
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4151    GCACGCCGCA TCCAGCGCTG ACGGAAGCAA AACACCAGCA GCAGTTTTTC
        CGTGCGGCGT AGGTCGCGAC TGCCTTCGTT TTGTGGTCGT CGTCAAAAAG
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4201    CAGTTCCGTT TATCCGGGCA AACCATCGAA GTGACCAGCG AATACCTGTT
        GTCAAGGCAA ATAGGCCCGT TTGGTAGCTT CACTGGTCGC TTATGGACAA
                              LacZ
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4251    CCGTCATAGC GATAACGAGC TCCTGCACTG GATGGTGGCG CTGGATGGTA
        GGCAGTATCG CTATTGCTCG AGGACGTGAC CTACCACCGC GACCTACCAT
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4301    AGCCGCTGGC AAGCGGTGAA GTGCCTCTGG ATGTCGCTCC ACAAGGTAAA
        TCGGCGACCG TTCGCCACTT CACGGAGACC TACAGCGAGG TGTTCCATTT
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4351    CAGTTGATTG AACTGCCTGA ACTACCGCAG CCGGAGAGCG CCGGGCAACT
        GTCAACTAAC TTGACGGACT TGATGGCGTC GGCCTCTCGC GGCCCGTTGA
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4401    CTGGCTCACA GTACGCGTAG TGCAACCGAA CGCGACCGCA TGGTCAGAAG
        GACCGAGTGT CATGCGCATC ACGTTGGCTT GCGCTGGCGT ACCAGTCTTC
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4451    CCGGGCACAT CAGCGCCTGG CAGCAGTGGC GTCTGGCGGA AAACCTCAGT
        GGCCCGTGTA GTCGCGGACC GTCGTCACCG CAGACCGCCT TTTGGAGTCA
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4501    GTGACGCTCC CCGCCGCGTC CCACGCCATC CCGCATCTGA CCACCAGCGA
        CACTGCGAGG GGCGGCGCAG GGTGCGGTAG GGCGTAGACT GGTGGTCGCT
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4551    AATGGATTTT TGCATCGAGC TGGGTAATAA GCGTTGGCAA TTTAACCGCC
        TTACCTAAAA ACGTAGCTCG ACCCATTATT CGCAACCGTT AAATTGGCGG
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4601    AGTCAGGCTT TCTTTCACAG ATGTGGATTG GCGATAAAAA ACAACTGCTG
        TCAGTCCGAA AGAAAGTGTC TACACCTAAC CGCTATTTTT TGTTGACGAC
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4651    ACGCCGCTGC GCGATCAGTT CACCCGTGCA CCGCTGGATA ACGACATTGG
        TGCGGCGACG CGCTAGTCAA GTGGGCACGT GGCGACCTAT TGCTGTAACC
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4701    CGTAAGTGAA GCGACCCGCA TTGACCCTAA CGCCTGGGTC GAACGCTGGA
        GCATTCACTT CGCTGGGCGT AACTGGGATT GCGGACCCAG CTTGCGACCT
                              LacZ
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4751    AGGCGGCGGG CCATTACCAG GCCGAAGCAG CGTTGTTGCA GTGCACGGCA
        TCCGCCGCCC GGTAATGGTC CGGCTTCGTC GCAACAACGT CACGTGCCGT
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                              LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4801  GATACACTTG CTGATGCGGT GCTGATTACG ACCGCTCACG CGTGGCAGCA
      CTATGTGAAC GACTACGCCA CGACTAATGC TGGCGAGTGC GCACCGTCGT
                              LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4851  TCAGGGGAAA ACCTTATTTA TCAGCCGGAA AACCTACCGG ATTGATGGTA
      AGTCCCCTTT TGGAATAAAT AGTCGGCCTT TTGGATGGCC TAACTACCAT
                              LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4901  GTGGTCAAAT GGCGATTACC GTTGATGTTG AAGTGGCGAG CGATACACCG
      CACCAGTTTA CCGCTAATGG CAACTACAAC TTCACCGCTC GCTATGTGGC
                              LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4951  CATCCGGCGC GGATTGGCCT GAACTGCCAG CTGGCGCAGG TAGCAGAGCG
      GTAGGCCGCG CCTAACCGGA CTTGACGGTC GACCGCGTCC ATCGTCTCGC
                              LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5001  GGTAAACTGG CTCGGATTAG GGCCGCAAGA AAACTATCCC GACCGCCTTA
      CCATTTGACC GAGCCTAATC CCGGCGTTCT TTTGATAGGG CTGGCGGAAT
                              LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5051  CTGCCGCCTG TTTTGACCGC TGGGATCTGC CATTGTCAGA CATGTATACC
      GACGGCGGAC AAAACTGGCG ACCCTAGACG GTAACAGTCT GTACATATGG
                              LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5101  CCGTACGTCT TCCCGAGCGA AAACGGTCTG CGCTGCGGGA CGCGCGAATT
      GGCATGCAGA AGGGCTCGCT TTTGCCAGAC GCGACGCCCT GCGCGCTTAA
                              LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5151  GAATTATGGC CCACACCAGT GGCGCGGCGA CTTCCAGTTC AACATCAGCC
      CTTAATACCG GGTGTGGTCA CCGCGCCGCT GAAGGTCAAG TTGTAGTCGG
                              LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5201  GGTACAGTCA ACAGCAATTG ATGGAAACCA GCCATTCGCC ATCTGCTGCA
      CCATGTCAGT TGTCGTTAAC TACCTTTGGT CGGTAAGCGG TAGACGACGT
                              LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5251  CGCGGAAGAG GCACATGGCT GAATATCGAC GGTTTCCATA TGGGGATTGG
      GCGCCTTCTC CGTGTACCGA CTTATAGCTG CCAAAGGTAT ACCCCTAACC
                              LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5301  TGGCGACGAC TCCTGGAGCC CGTCAGTATC GGCGGAATTC CAGCTGAGCG
      ACCGCTGCTG AGGACCTCGG GCAGTCATAG CCGCCTTAAG GTCGACTCGC
                         LacZ
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5351  CCGGTCGCTA CCATTACCAG TTGGTCTGGT GTCAAAAATA ATAATAACCG
      GGCCAGCGAT GGTAATGGTC AACCAGACCA CAGTTTTTAT TATTATTGGC
5401  GGCAGGGGGG ATCCGGAGCT TATCGCAGAT CAATTCGATA TCAAGCTTAT
      CCGTCCCCCC TAGGCCTCGA ATAGCGTCTA GTTAAGCTAT AGTTCGAATA
                                              H6  Promoter
                                              ~~~~~~~~~~~~~~~
5451  CGATACCGTC GACGGTATCG ATAAGCTCTA GTGGAGGGTT CTTTATTCTA
      GCTATGGCAG CTGCCATAGC TATTCGAGAT CACCTCCCAA GAAATAAGAT
                         H6  Promoter
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5501  TACTTAAAAA GTGAAAATAA ATACAAAGGT TCTTGAGGGT TGTGTTAAAT
      ATGAATTTTT CACTTTTATT TATGTTTCCA AGAACTCCCA ACACAATTTA
                          H6  Promoter
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

5551  TGAAAGCGAG AAATAATCAT AAATTATTTC ATTATCGCGA TATCCGTTAA
      ACTTTCGCTC TTTATTAGTA TTTAATAAAG TAATAGCGCT ATAGGCAATT
       H6  Promoter                          NYESO-1
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5601  GTTTGTATCG TACCCCCCCC GAGCCATGCA GGCCGAAGGC CGGGGCACAG
      CAAACATAGC ATGGGGGGGG CTCGGTACGT CCGGCTTCCG GCCCCGTGTC
                             NYESO-1
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5651  GGGGTTCGAC GGGCGATGCT GATGGCCCAG GAGGCCCTGG CATTCCTGAT
      CCCCAAGCTG CCCGCTACGA CTACCGGGTC CTCCGGGACC GTAAGGACTA
                             NYESO-1
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5701  GGCCCAGGGG GCAATGCTGG CGGCCCAGGA GAGGCGGGTG CCACGGGCGG
      CCGGGTCCCC CGTTACGACC GCCGGGTCCT CTCCGCCCAC GGTGCCCGCC
                             NYESO-1
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5751  CAGAGGTCCC CGGGGCGCAG GGGCAGCAAG GGCCTCGGGG CCGGGAGGAG
      GTCTCCAGGG GCCCCGCGTC CCCGTCGTTC CCGGAGCCCC GGCCCTCCTC
                             NYESO-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

5801  GCGCCCCGCG GGGTCCGCAT GGCGGCGCGG CTTCAGGGCT GAATGGATGC
      CGCGGGGCGC CCCAGGCGTA CCGCCGCGCC GAAGTCCCGA CTTACCTACG
                             NYESO-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

5851  TGCAGATGCG GGGCCAGGGG GCCGGAGAGC CGCCTGCTTG AGTTCTACCT
      ACGTCTACGC CCCGGTCCCC CGGCCTCTCG GCGGACGAAC TCAAGATGGA
                             NYESO-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

5901  CGCCATGCCT TTCGCGACAC CCATGGAAGC AGAGCTGGCC CGCAGGAGCC
      GCGGTACGGA AAGCGCTGTG GGTACCTTCG TCTCGACCGG GCGTCCTCGG
                             NYESO-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

5951  TGGCCCAGGA TGCCCCACCG CTTCCCGTGC CAGGGGTGCT TCTGAAGGAG
      ACCGGGTCCT ACGGGGTGGC GAAGGGCACG GTCCCCACGA AGACTTCCTC
                             NYESO-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

6001  TTCACTGTGT CCGGCAACAT ACTGACTATC CGACTGACTG CTGCAGACCA
      AAGTGACACA GGCCGTTGTA TGACTGATAG GCTGACTGAC GACGTCTGGT
                             NYESO-1
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6051  CCGCCAACTG CAGCTCTCCA TCAGCTCCTG TCTCCAGCAG CTTTCCCTGT
      GGCGGTTGAC GTCGAGAGGT AGTCGAGGAC AGAGGTCGTC GAAAGGGACA
                             NYESO-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

6101  TGATGTGGAT CACGCAGGTG TTTCTGCCCG TGTTTTTGGC TCAGCCTCCC
      ACTACACCTA GTGCGTCCAC AAAGACGGGC ACAAAAACCG AGTCGGAGGG
                 NYESO-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~

6151  TCAGGGCAGA GGCGCTAAGT AATTAATTTT TTTTTGGGCT GCAGGATCGC
      AGTCCCGTCT CCGCGATTCA TTAATTAAAA AAAAACCCGA CGTCCTAGCG
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                                 sE/L Promoter
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6201   TAGCAAAAAT TGAAATTTTA TTTTTTTTTT TTGGAATATA AATAAGCTCG
       ATCGTTTTTA ACTTTAAAAT AAAAAAAAAA AACCTTATAT TTATTCGAGC
                                         hTRP-2
                          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
       sE/L Promoter
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6251   AAGCTCGAGC CATGAGCCCC CTTTGGTGGG GGTTTCTGCT CAGTTGCTTG
       TTCGAGCTCG GTACTCGGGG GAAACCACCC CCAAAGACGA GTCAACGAAC
                              hTRP-2
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6301   GGCTGCAAAA TCCTGCCAGG AGCCCAGGGT CAGTTCCCCC GAGTCTGCAT
       CCGACGTTTT AGGACGGTCC TCGGGTCCCA GTCAAGGGGG CTCAGACGTA
                              hTRP-2
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6351   GACGGTGGAC AGCCTAGTGA ACAAGGAGTG CTGCCCACGC CTGGGTGCAG
       CTGCCACCTG TCGGATCACT TGTTCCTCAC GACGGGTGCG GACCCACGTC
                              hTRP-2
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6401   AGTCGGCCAA TGTCTGTGGC TCTCAGCAAG GCCGGGGGCA GTGCACAGAG
       TCAGCCGGTT ACAGACACCG AGAGTCGTTC CGGCCCCCGT CACGTGTCTC
                              hTRP-2
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6451   GTGCGAGCCG ACACAAGGCC CTGGAGTGGT CCCTACATCC TACGAAACCA
       CACGCTCGGC TGTGTTCCGG GACCTCACCA GGGATGTAGG ATGCTTTGGT
                              hTRP-2
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6501   GGATGACCGT GAGCTGTGGC CAAGAAAATT CTTCCACCGG ACCTGCAAGT
       CCTACTGGCA CTCGACACCG GTTCTTTTAA GAAGGTGGCC TGGACGTTCA
                              hTRP-2
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6551   GCACAGGAAA CTTTGCCGGC TATAATTGTG GAGACTGCAA GTTTGGCTGG
       CGTGTCCTTT GAAACGGCCG ATATTAACAC CTCTGACGTT CAAACCGACC
                              hTRP-2
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6601   ACCGGTCCCA ACTGCGAGCG GAAGAAACCA CCAGTGATTC GGCAGAACAT
       TGGCCAGGGT TGACGCTCGC CTTCTTTGGT GGTCACTAAG CCGTCTTGTA
                              hTRP-2
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6651   CCATTCCTTG AGTCCTCAGG AAAGAGAGCA GTTCTTGGGC GCCTTAGATC
       GGTAAGGAAC TCAGGAGTCC TTTCTCTCGT CAAGAACCCG CGGAATCTAG
                              hTRP-2
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6701   TCGCGAAGAA GAGAGTACAC CCCGACTACG TGATCACCAC ACAACACTGG
       AGCGCTTCTT CTCTCATGTG GGGCTGATGC ACTAGTGGTG TGTTGTGACC
                              hTRP-2
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6751   CTGGGCCTGC TTGGGCCCAA TGGAACCCAG CCGCAGTTTG CCAACTGCAG
       GACCCGGACG AACCCGGGTT ACCTTGGGTC GGCGTCAAAC GGTTGACGTC
                              hTRP-2
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6801   TGTTTATGAT TTCTTCGTGT GGCTCCATTA TTATTCTGTT AGAGATACAT
       ACAAATACTA AAGAAGCACA CCGAGGTAAT AATAAGACAA TCTCTATGTA
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                         hTRP-2
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6851 TATTAGGACC AGGACGCCCC TACAGGGCCA TAGATTTCTC ACATCAAGGA
     ATAATCCTGG TCCTGCGGGG ATGTCCCGGT ATCTAAAGAG TGTAGTTCCT
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6901 CCTGCATTTG TTACCTGGCA CCGGTACCAT TTGTTGTGTC TGGAAAGAGA
     GGACGTAAAC AATGGACCGT GGCCATGGTA AACAACACAG ACCTTTCTCT
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6951 TCTCCAGCGA CTCATTGGCA ATGAGTCTTT TGCTTTGCCC TACTGGAACT
     AGAGGTCGCT GAGTAACCGT TACTCAGAAA ACGAAACGGG ATGACCTTGA
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7001 TTGCCACTGG GAGGAACGAG TGTGATGTGT GTACAGACCA GCTGTTTGGG
     AACGGTGACC CTCCTTGCTC ACACTACACA CATGTCTGGT CGACAAACCC
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7051 GCAGCGAGAC CAGACGATCC GACTCTGATT AGTCGGAACT CAAGATTCTC
     CGTCGCTCTG GTCTGCTAGG CTGAGACTAA TCAGCCTTGA GTTCTAAGAG
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7101 CAGCTGGGAA ACTGTCTGTG ATAGCTTGGA TGACTACAAC CACCTGGTCA
     GTCGACCCTT TGACAGACAC TATCGAACCT ACTGATGTTG GTGGACCAGT
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7151 CCTTGTGCAA TGGAACCTAT GAAGGTTTGC TGAGAAGAAA TCAAATGGGA
     GGAACACGTT ACCTTGGATA CTTCCAAACG ACTCTTCTTT AGTTTACCCT
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7201 AGAAACAGCA TGAAATTGCC AACCTTAAAA GACATACGAG ATTGCCTGTC
     TCTTTGTCGT ACTTTAACGG TTGGAATTTT CTGTATGCTC TAACGGACAG
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7251 TCTCCAGAAG TTTGACAATC CTCCCTTCTT CCAGAACTCT ACCTTCAGTT
     AGAGGTCTTC AAACTGTTAG GAGGGAAGAA GGTCTTGAGA TGGAAGTCAA
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7301 TCAGGAATGC TTTGGAAGGG TTTGATAAAG CAGATGGGAC TCTGGATTCT
     AGTCCTTACG AAACCTTCCC AAACTATTTC GTCTACCCTG AGACCTAAGA
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7351 CAAGTGATGA GCCTTCATAA TTTGGTTCAT TCCTTCCTGA ACGGGACAAA
     GTTCACTACT CGGAAGTATT AAACCAAGTA AGGAAGGACT TGCCCTGTTT
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7401 CGCTTTGCCA CATTCAGCCG CCAATGATCC CATCTTCGTG GTGATTTCTA
     GCGAAACGGT GTAAGTCGGC GGTTACTAGG GTAGAAGCAC CACTAAAGAT
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7451 ATCGTTTGCT TTACAATGCT ACAACAAACA TCCTTGAACA TGTAAGAAAA
     TAGCAAACGA AATGTTACGA TGTTGTTTGT AGGAACTTGT ACATTCTTTT
                         hTRP-2
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7501 GAGAAAGCGA CCAAGGAACT CCCTTCCCTG CATGTGCTGG TTCTTCATTC
     CTCTTTCGCT GGTTCCTTGA GGGAAGGGAC GTACACGACC AAGAAGTAAG
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                                hTRP-2
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7551  CTTTACTGAT GCCATCTTTG ATGAGTGGAT GAAAAGATTT AATCCTCCTG
      GAAATGACTA CGGTAGAAAC TACTCACCTA CTTTTCTAAA TTAGGAGGAC
                                hTRP-2
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7601  CAGATGCCTG GCCTCAGGAG CTGGCCCCTA TTGGTCACAA TCGGATGTAC
      GTCTACGGAC CGGAGTCCTC GACCGGGGAT AACCAGTGTT AGCCTACATG
                                hTRP-2
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7651  AACATGGTTC CTTTCTTCCC TCCAGTGACT AATGAAGAAC TCTTTTTAAC
      TTGTACCAAG GAAAGAAGGG AGGTCACTGA TTACTTCTTG AGAAAAATTG
                                hTRP-2
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7701  CTCAGACCAA CTTGGCTACA GCTATGCCAT CGATCTGCCA GTTTCAGTTG
      GAGTCTGGTT GAACCGATGT CGATACGGTA GCTAGACGGT CAAAGTCAAC
                                hTRP-2
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7751  AAGAAACTCC AGGTTGGCCC ACAACTCTCT TAGTAGTCAT GGGAACACTG
      TTCTTTGAGG TCCAACCGGG TGTTGAGAGA ATCATCAGTA CCCTTGTGAC
                                hTRP-2
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7801  GTGGCTTTGG TTGGTCTGTT CGTGCTGTTG GCTTTTCTTC AATATAGAAG
      CACCGAAACC AACCAGACAA GCACGACAAC CGAAAAGAAG TTATATCTTC
                                hTRP-2
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7851  ACTTCGAAAA GGATATACAC CCCTAATGGA GACACATTTA AGCAGCAAGA
      TGAAGCTTTT CCTATATGTG GGGATTACCT CTGTGTAAAT TCGTCGTTCT
                hTRP-2
      ~~~~~~~~~~~~~~~~~~~~~~
7901  GATACACAGA AGAAGCCTAG TTTTTTAATT AAGCATGCTC TAGAATCGAT
      CTATGTGTCT TCTTCGGATC AAAAAATTAA TTCGTACGAG ATCTTAGCTA
                                                C5 Left Arm
                                             ~~~~~~~~~~~~~~~~~~~~
7951  CCCGGGTTTT TATGACTAGT TAATCACGGC CGCTTATAAA GATCTAAAAT
      GGGCCCAAAA ATACTGATCA ATTAGTGCCG GCGAATATTT CTAGATTTTA
                              C5 Left Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8001  GCATAATTTC TAAATAATGA AAAAAAAGTA CATCATGAGC AACGCGTTAG
      CGTATTAAAG ATTTATTACT TTTTTTTCAT GTAGTACTCG TTGCGCAATC
                              C5 Left Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8051  TATATTTTAC AATGGAGATT AACGCTCTAT ACCGTTCTAT GTTTATTGAT
      ATATAAAATG TTACCTCTAA TTGCGAGATA TGGCAAGATA CAAATAACTA
                              C5 Left Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8101  TCAGATGATG TTTTAGAAAA GAAAGTTATT GAATATGAAA ACTTTAATGA
      AGTCTACTAC AAAATCTTTT CTTTCAATAA CTTATACTTT TGAAATTACT
                              C5 Left Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8151  AGATGAAGAT GACGACGATG ATTATTGTTG TAAATCTGTT TTAGATGAAG
      TCTACTTCTA CTGCTGCTAC TAATAACAAC ATTTAGACAA AATCTACTTC
                              C5 Left Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8201  AAGATGACGC GCTAAAGTAT ACTATGGTTA CAAAGTATAA GTCTATACTA
      TTCTACTGCG CGATTTCATA TGATACCAAT GTTTCATATT CAGATATGAT
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                     C5 Left Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8251  CTAATGGCGA CTTGTGCAAG AAGGTATAGT ATAGTGAAAA TGTTGTTAGA
      GATTACCGCT GAACACGTTC TTCCATATCA TATCACTTTT ACAACAATCT
                     C5 Left Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8301  TTATGATTAT GAAAAACCAA ATAAATCAGA TCCATATCTA AAGGTATCTC
      AATACTAATA CTTTTTGGTT TATTTAGTCT AGGTATAGAT TTCCATAGAG
                     C5 Left Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8351  CTTTGCACAT AATTTCATCT ATTCCTAGTT TAGAATACTT TTCATTATAT
      GAAACGTGTA TTAAAGTAGA TAAGGATCAA ATCTTATGAA AAGTAATATA
                     C5 Left Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8401  TTGTTTACAG CTGAAGACGA AAAAAATATA TCGATAATAG AAGATTATGT
      AACAAATGTC GACTTCTGCT TTTTTTATAT AGCTATTATC TTCTAATACA
                  C5 Left Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8451  TAACTCTGCT AATAAGATGA AATTGAATGA GTCTGTGACT GCAGCCAAGC
      ATTGAGACGA TTATTCTACT TTAACTTACT CAGACACTGA CGTCGGTTCG
8501  TTGGCACTGG CCGTCGTTTT ACAACGTCGT GACTGGGAAA ACCCTGGCGT
      AACCGTGACC GGCAGCAAAA TGTTGCAGCA CTGACCCTTT TGGGACCGCA
8551  TACCCAACTT AATCGCCTTG CAGCACATCC CCCTTTCGCC AGCTGGCGTA
      ATGGGTTGAA TTAGCGGAAC GTCGTGTAGG GGGAAAGCGG TCGACCGCAT
8601  ATAGCGAAGA GGCCCGCACC GATCGCCCTT CCCAACAGTT GCGCAGCCTG
      TATCGCTTCT CCGGGCGTGG CTAGCGGGAA GGGTTGTCAA CGCGTCGGAC
8651  AATGGCGAAT GGCGCCTGAT GCGGTATTTT CTCCTTACGC ATCTGTGCGG
      TTACCGCTTA CCGCGGACTA CGCCATAAAA GAGGAATGCG TAGACACGCC
8701  TATTTCACAC CGCATATGGT GCACTCTCAG TACAATCTGC TCTGATGCCG
      ATAAAGTGTG GCGTATACCA CGTGAGAGTC ATGTTAGACG AGACTACGGC
8751  CATAGTTAAG CCAGCCCCGA CACCCGCCAA CACCCGCTGA CGCGCCCTGA
      GTATCAATTC GGTCGGGGCT GTGGGCGGTT GTGGGCGACT GCGCGGGACT
8801  CGGGCTTGTC TGCTCCCGGC ATCCGCTTAC AGACAAGCTG TGACCGTCTC
      GCCCGAACAG ACGAGGGCCG TAGGCGAATG TCTGTTCGAC ACTGGCAGAG
8851  CGGGAGCTGC ATGTGTCAGA GGTTTTCACC GTCATCACCG AAACGCGCGA
      GCCCTCGACG TACACAGTCT CCAAAAGTGG CAGTAGTGGC TTTGCGCGCT
8901  GACGAAAGGG CCTCGTGATA CGCCTATTTT TATAGGTTAA TGTCATGATA
      CTGCTTTCCC GGAGCACTAT GCGGATAAAA ATATCCAATT ACAGTACTAT
8951  ATAATGGTTT CTTAGACGTC AGGTGGCACT TTTCGGGGAA ATGTGCGCGG
      TATTACCAAA GAATCTGCAG TCCACCGTGA AAAGCCCCTT TACACGCGCC
9001  AACCCCTATT TGTTTATTTT TCTAAATACA TTCAAATATG TATCCGCTCA
      TTGGGGATAA ACAAATAAAA AGATTTATGT AAGTTTATAC ATAGGCGAGT
9051  TGAGACAATA ACCCTGATAA ATGCTTCAAT AATATTGAAA AAGGAAGAGT
      ACTCTGTTAT TGGGACTATT TACGAAGTTA TTATAACTTT TTCCTTCTCA
                          Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9101  ATGAGTATTC AACATTTCCG TGTCGCCCTT ATTCCCTTTT TTGCGGCATT
      TACTCATAAG TTGTAAAGGC ACAGCGGGAA TAAGGGAAAA AACGCCGTAA
                          Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9151  TTGCCTTCCT GTTTTTGCTC ACCCAGAAAC GCTGGTGAAA GTAAAAGATG
      AACGGAAGGA CAAAAACGAG TGGGTCTTTG CGACCACTTT CATTTTCTAC
                          Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9201  CTGAAGATCA GTTGGGTGCA CGAGTGGGTT ACATCGAACT GGATCTCAAC
      GACTTCTAGT CAACCCACGT GCTCACCCAA TGTAGCTTGA CCTAGAGTTG
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                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9251    AGCGGTAAGA TCCTTGAGAG TTTTCGCCCC GAAGAACGTT TTCCAATGAT
        TCGCCATTCT AGGAACTCTC AAAAGCGGGG CTTCTTGCAA AAGGTTACTA
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9301    GAGCACTTTT AAAGTTCTGC TATGTGGCGC GGTATTATCC CGTATTGACG
        CTCGTGAAAA TTTCAAGACG ATACACCGCG CCATAATAGG GCATAACTGC
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9351    CCGGGCAAGA GCAACTCGGT CGCCGCATAC ACTATTCTCA GAATGACTTG
        GGCCCGTTCT CGTTGAGCCA GCGGCGTATG TGATAAGAGT CTTACTGAAC
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9401    GTTGAGTACT CACCAGTCAC AGAAAAGCAT CTTACGGATG GCATGACAGT
        CAACTCATGA GTGGTCAGTG TCTTTTCGTA GAATGCCTAC CGTACTGTCA
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9451    AAGAGAATTA TGCAGTGCTG CCATAACCAT GAGTGATAAC ACTGCGGCCA
        TTCTCTTAAT ACGTCACGAC GGTATTGGTA CTCACTATTG TGACGCCGGT
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9501    ACTTACTTCT GACAACGATC GGAGGACCGA AGGAGCTAAC CGCTTTTTTG
        TGAATGAAGA CTGTTGCTAG CCTCCTGGCT TCCTCGATTG GCGAAAAAAC
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9551    CACAACATGG GGGATCATGT AACTCGCCTT GATCGTTGGG AACCGGAGCT
        GTGTTGTACC CCCTAGTACA TTGAGCGGAA CTAGCAACCC TTGGCCTCGA
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9601    GAATGAAGCC ATACCAAACG ACGAGCGTGA CACCACGATG CCTGTAGCAA
        CTTACTTCGG TATGGTTTGC TGCTCGCACT GTGGTGCTAC GGACATCGTT
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9651    TGGCAACAAC GTTGCGCAAA CTATTAACTG GCGAACTACT TACTCTAGCT
        ACCGTTGTTG CAACGCGTTT GATAATTGAC CGCTTGATGA ATGAGATCGA
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9701    TCCCGGCAAC AATTAATAGA CTGGATGGAG GCGGATAAAG TTGCAGGACC
        AGGGCCGTTG TTAATTATCT GACCTACCTC CGCCTATTTC AACGTCCTGG
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9751    ACTTCTGCGC TCGGCCCTTC CGGCTGGCTG GTTTATTGCT GATAAATCTG
        TGAAGACGCG AGCCGGGAAG GCCGACCGAC CAAATAACGA CTATTTAGAC
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9801    GAGCCGGTGA GCGTGGGTCT CGCGGTATCA TTGCAGCACT GGGGCCAGAT
        CTCGGCCACT CGCACCCAGA GCGCCATAGT AACGTCGTGA CCCCGGTCTA
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9851    GGTAAGCCCT CCCGTATCGT AGTTATCTAC ACGACGGGGA GTCAGGCAAC
        CCATTCGGGA GGGCATAGCA TCAATAGATG TGCTGCCCCT CAGTCCGTTG
                               Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9901    TATGGATGAA CGAAATAGAC AGATCGCTGA GATAGGTGCC TCACTGATTA
        ATACCTACTT GCTTTATCTG TCTAGCGACT CTATCCACGG AGTGACTAAT
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       Amp(R)
       ~~~~~~~~~~~~~
 9951  AGCATTGGTA ACTGTCAGAC CAAGTTTACT CATATATACT TTAGATTGAT
       TCGTAACCAT TGACAGTCTG GTTCAAATGA GTATATATGA AATCTAACTA
10001  TTAAAACTTC ATTTTTAATT TAAAAGGATC TAGGTGAAGA TCCTTTTTGA
       AATTTTGAAG TAAAAATTAA ATTTTCCTAG ATCCACTTCT AGGAAAAACT
10051  TAATCTCATG ACCAAAATCC CTTAACGTGA GTTTTCGTTC CACTGAGCGT
       ATTAGAGTAC TGGTTTTAGG GAATTGCACT CAAAAGCAAG GTGACTCGCA
10101  CAGACCCCGT AGAAAAGATC AAAGGATCTT CTTGAGATCC TTTTTTTCTG
       GTCTGGGGCA TCTTTTCTAG TTTCCTAGAA GAACTCTAGG AAAAAAAGAC
10151  CGCGTAATCT GCTGCTTGCA AACAAAAAAA CCACCGCTAC CAGCGGTGGT
       GCGCATTAGA CGACGAACGT TTGTTTTTTT GGTGGCGATG GTCGCCACCA
10201  TTGTTTGCCG GATCAAGAGC TACCAACTCT TTTTCCGAAG GTAACTGGCT
       AACAAACGGC CTAGTTCTCG ATGGTTGAGA AAAAGGCTTC CATTGACCGA
10251  TCAGCAGAGC GCAGATACCA AATACTGTCC TTCTAGTGTA GCCGTAGTTA
       AGTCGTCTCG CGTCTATGGT TTATGACAGG AAGATCACAT CGGCATCAAT
10301  GGCCACCACT TCAAGAACTC TGTAGCACCG CCTACATACC TCGCTCTGCT
       CCGGTGGTGA AGTTCTTGAG ACATCGTGGC GGATGTATGG AGCGAGACGA
10351  AATCCTGTTA CCAGTGGCTG CTGCCAGTGG CGATAAGTCG TGTCTTACCG
       TTAGGACAAT GGTCACCGAC GACGGTCACC GCTATTCAGC ACAGAATGGC
10401  GGTTGGACTC AAGACGATAG TTACCGGATA AGGCGCAGCG GTCGGGCTGA
       CCAACCTGAG TTCTGCTATC AATGGCCTAT TCCGCGTCGC CAGCCCGACT
10451  ACGGGGGGTT CGTGCACACA GCCCAGCTTG GAGCGAACGA CCTACACCGA
       TGCCCCCCAA GCACGTGTGT CGGGTCGAAC CTCGCTTGCT GGATGTGGCT
10501  ACTGAGATAC CTACAGCGTG AGCTATGAGA AAGCGCCACG CTTCCCGAAG
       TGACTCTATG GATGTCGCAC TCGATACTCT TTCGCGGTGC GAAGGGCTTC
10551  GGAGAAAGGC GGACAGGTAT CCGGTAAGCG GCAGGGTCGG AACAGGAGAG
       CCTCTTTCCG CCTGTCCATA GGCCATTCGC CGTCCCAGCC TTGTCCTCTC
10601  CGCACGAGGG AGCTTCCAGG GGGAAACGCC TGGTATCTTT ATAGTCCTGT
       GCGTGCTCCC TCGAAGGTCC CCCTTTGCGG ACCATAGAAA TATCAGGACA
10651  CGGGTTTCGC CACCTCTGAC TTGAGCGTCG ATTTTTGTGA TGCTCGTCAG
       GCCCAAAGCG GTGGAGACTG AACTCGCAGC TAAAAACACT ACGAGCAGTC
10701  GGGGGCGGAG CCTATGGAAA AACGCCAGCA ACGCGGCCTT TTTACGGTTC
       CCCCCGCCTC GGATACCTTT TTGCGGTCGT TGCGCCGGAA AAATGCCAAG
10751  CTGGCCTTTT GCTGGCCTTT TGCTCACATG TTCTTTCCTG CGTTATCCCC
       GACCGGAAAA CGACCGGAAA ACGAGTGTAC AAGAAAGGAC GCAATAGGGG
10801  TGATTCTGTG GATAACCGTA TTACCGCCTT TGAGTGAGCT GATACCGCTC
       ACTAAGACAC CTATTGGCAT AATGGCGGAA ACTCACTCGA CTATGGCGAG
10851  GCCGCAGCCG AACGACCGAG CGCAGCGAGT CAGTGAGCGA GGAAGCGGAA
       CGGCGTCGGC TTGCTGGCTC GCGTCGCTCA GTCACTCGCT CCTTCGCCTT
10901  GAGCGCCCAA TACGCAAACC GCCTCTCCCC GCGCGTTGGC CGATTCATTA
       CTCGCGGGTT ATGCGTTTGG CGGAGAGGGG CGCGCAACCG GCTAAGTAAT
10951  ATGCAGCTGG CACGACAGGT TTCCCGACTG GAAAGCGGGC AGTGAGCGCA
       TACGTCGACC GTGCTGTCCA AAGGGCTGAC CTTTCGCCCG TCACTCGCGT
11001  ACGCAATTAA TGTGAGTTAG CTCACTCATT AGGCACCCCA GGCTTTACAC
       TGCGTTAATT ACACTCAATC GAGTGAGTAA TCCGTGGGGT CCGAAATGTG
11051  TTTATGCTTC CGGCTCGTAT GTTGTGTGGA ATTGTGAGCG GATAACAATT
       AAATACGAAG GCCGAGCATA CAACACACCT TAACACTCGC CTATTGTTAA
11101  TCACACAGGA AACAGCTATG ACCATGATTA CGAATTGAAT TGCGGCCGCA
       AGTGTGTCCT TTGTCGATAC TGGTACTAAT GCTTAACTTA ACGCCGGCGT
11151  ATTCTAAG
```

FIGURE 4

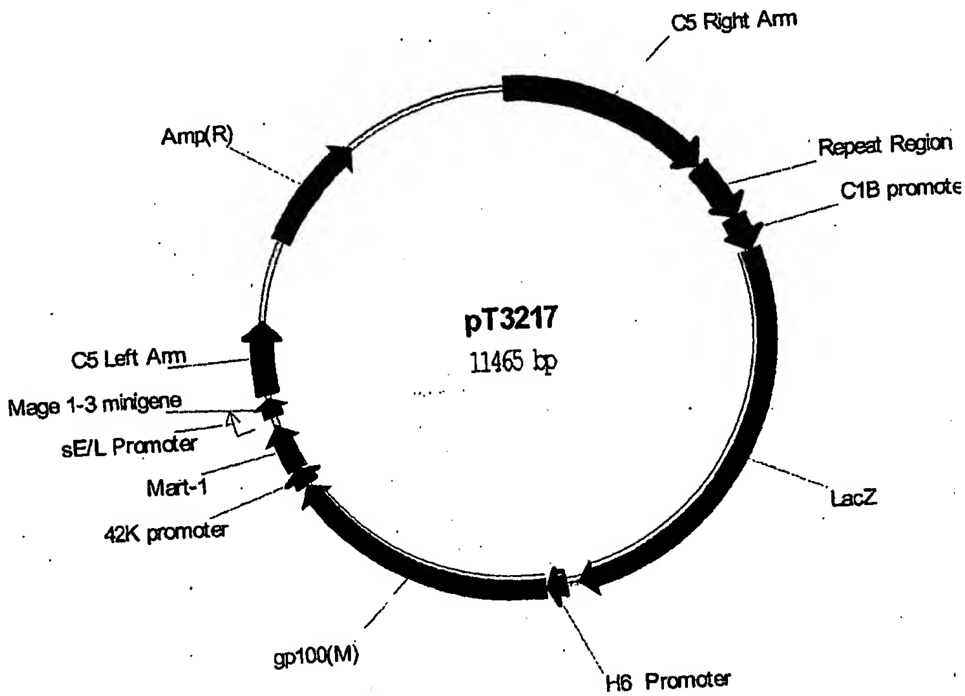
C5 Right Arm
Repeat Region
C1B promote
LacZ
H6 Promoter
gp100(M)
42K promoter
Mart-1
sE/L Promoter
Mage 1-3 minigene
C5 Left Arm
Amp(R)
pT3217
11465 bp

FIGURE 5

DNA Sequence of donor plasmid pT3217

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                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   1    TGAATGTTAA ATGTTATACT TTGGATGAAG CTATAAATAT GCATTGGAAA
        ACTTACAATT TACAATATGA AACCTACTTC GATATTTATA CGTAACCTTT
                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  51    AATAATCCAT TTAAAGAAAG GATTCAAATA CTACAAAACC TAAGCGATAA
        TTATTAGGTA AATTTCTTTC CTAAGTTTAT GATGTTTTGG ATTCGCTATT
                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 101    TATGTTAACT AAGCTTATTC TTAACGACGC TTTAAATATA CACAAATAAA
        ATACAATTGA TTCGAATAAG AATTGCTGCG AAATTTATAT GTGTTTATTT
                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 151    CATAATTTTT GTATAACCTA ACAAATAACT AAAACATAAA AATAATAAAA
        GTATTAAAAA CATATTGGAT TGTTTATTGA TTTTGTATTT TTATTATTTT
                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 201    GGAAATGTAA TATCGTAATT ATTTTACTCA GGAATGGGGT TAAATATTTA
        CCTTTACATT ATAGCATTAA TAAAATGAGT CCTTACCCCA ATTTATAAAT
                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 251    TATCACGTGT ATATCTATAC TGTTATCGTA TACTCTTTAC AATTACTATT
        ATAGTGCACA TATAGATATG ACAATAGCAT ATGAGAAATG TTAATGATAA
                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 301    ACGAATATGC AAGAGATAAT AAGATTACGT ATTTAAGAGA ATCTTGTCAT
        TGCTTATACG TTCTCTATTA TTCTAATGCA TAAATTCTCT TAGAACAGTA
                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 351    GATAATTGGG TACGACATAG TGATAAATGC TATTTCGCAT CGTTACATAA
        CTATTAACCC ATGCTGTATC ACTATTTACG ATAAAGCGTA GCAATGTATT
                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 401    AGTCAGTTGG AAAGATGGAT TTGACAGATG TAACTTAATA GGTGCAAAAA
        TCAGTCAACC TTTCTACCTA AACTGTCTAC ATTGAATTAT CCACGTTTTT
                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 451    TGTTAAATAA CAGCATTCTA TCGGAAGATA GGATACCAGT TATATTATAC
        ACAATTTATT GTCGTAAGAT AGCCTTCTAT CCTATGGTCA ATATAATATG
                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 501    AAAAATCACT GGTTGGATAA AACAGATTCT GCAATATTCG TAAAAGATGA
        TTTTTAGTGA CCAACCTATT TTGTCTAAGA CGTTATAAGC ATTTTCTACT
                                C5 Right Arm
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 551    AGATTACTGC GAATTTGTAA ACTATGACAA TAAAAAGCCA TTTATCTCAA
        TCTAATGACG CTTAAACATT TGATACTGTT ATTTTTCGGT AAATAGAGTT
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                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 601  CGACATCGTG TAATTCTTCC ATGTTTTATG TATGTGTTTC AGATATTATG
      GCTGTAGCAC ATTAAGAAGG TACAAAATAC ATACACAAAG TCTATAATAC
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 651  AGATTACTAT AAACTTTTTG TATACTTATA TTCCGTAAAC TATATTAATC
      TCTAATGATA TTTGAAAAAC ATATGAATAT AAGGCATTTG ATATAATTAG
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 701  ATGAAGAAAA TGAAAAAGTA TAGAAGCTGT TCACGAGCGG TTGTTGAAAA
      TACTTCTTTT ACTTTTTCAT ATCTTCGACA AGTGCTCGCC AACAACTTTT
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 751  CAACAAAATT ATACATTCAA GATGGCTTAC ATATACGTCT GTGAGGCTAT
      GTTGTTTTAA TATGTAAGTT CTACCGAATG TATATGCAGA CACTCCGATA
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 801  CATGGATAAT GACAATGCAT CTCTAAATAG GTTTTTGGAC AATGGATTCG
      GTACCTATTA CTGTTACGTA GAGATTTATC CAAAAACCTG TTACCTAAGC
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 851  ACCCTAACAC GGAATATGGT ACTCTACAAT CTCCTCTTGA AATGGCTGTA
      TGGGATTGTG CCTTATACCA TGAGATGTTA GAGGAGAACT TTACCGACAT
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 901  ATGTTCAAGA ATACCGAGGC TATAAAAATC TTGATGAGGT ATGGAGCTAA
      TACAAGTTCT TATGGCTCCG ATATTTTTAG AACTACTCCA TACCTCGATT
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 951  ACCTGTAGTT ACTGAATGCA CAACTTCTTG TCTGCATGAT GCGGTGTTGA
      TGGACATCAA TGACTTACGT GTTGAAGAAC AGACGTACTA CGCCACAACT
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1001  GAGACGACTA CAAAATAGTG AAAGATCTGT TGAAGAATAA CTATGTAAAC
      CTCTGCTGAT GTTTTATCAC TTTCTAGACA ACTTCTTATT GATACATTTG
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1051  AATGTTCTTT ACAGCGGAGG CTTTACTCCT TTGTGTTTGG CAGCTTACCT
      TTACAAGAAA TGTCGCCTCC GAAATGAGGA AACACAAACC GTCGAATGGA
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1101  TAACAAAGTT AATTTGGTTA AACTTCTATT GGCTCATTCG GCGGATGTAG
      ATTGTTTCAA TTAAACCAAT TTGAAGATAA CCGAGTAAGC CGCCTACATC
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1151  ATATTTCAAA CACGGATCGG TTAACTCCTC TACATATAGC CGTATCAAAT
      TATAAAGTTT GTGCCTAGCC AATTGAGGAG ATGTATATCG GCATAGTTTA
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1201  AAAAATTTAA CAATGGTTAA ACTTCTATTG AACAAAGGTG CTGATACTGA
      TTTTTAAATT GTTACCAATT TGAAGATAAC TTGTTTCCAC GACTATGACT
                    C5 Right Arm
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1251  CTTGCTGGAT AACATGGGAT GTACTCCTTT AATGATCGCT GTACAATCTG
      GAACGACCTA TTGTACCCTA CATGAGGAAA TTACTAGCGA CATGTTAGAC
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                      C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1301      GAAATATTGA AATATGTAGC ACACTACTTA AAAAAAATAA AATGTCCAGA
          CTTTATAACT TTATACATCG TGTGATGAAT TTTTTTTATT TTACAGGTCT
                      C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1351      ACTGGGAAAA ATTGATCTTG CCAGCTGTAA TTCATGGTAG AAAAGAAGTG
          TGACCCTTTT TAACTAGAAC GGTCGACATT AAGTACCATC TTTTCTTCAC
                      C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1401      CTCAGGCTAC TTTTCAACAA AGGAGCAGAT GTAAACTACA TCTTTGAAAG
          GAGTCCGATG AAAAGTTGTT TCCTCGTCTA CATTTGATGT AGAAACTTTC
                      C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1451      AAATGGAAAA TCATATACTG TTTTGGAATT GATTAAAGAA AGTTACTCTG
          TTTACCTTTT AGTATATGAC AAAACCTTAA CTAATTTCTT TCAATGAGAC
                  C5 Right Arm
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1501      AGACACAAAA GAGGTAGCTG AAGTGGTACT CTCAAAGGTA CGTGACTAAT
          TCTGTGTTTT CTCCATCGAC TTCACCATGA GAGTTTCCAT GCACTGATTA
                                       Repeat Region
                                ~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1551      TAGCTATAAA AAGGATCGGG TTCTTTATTC TATACTTAAA AAGTGAAAAT
          ATCGATATTT TTCCTAGCCC AAGAAATAAG ATATGAATTT TTCACTTTTA
                      Repeat Region
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1601      AAATACAAAG GTTCTTGAGG GTTGTGTTAA ATTGAAAGCG AGAAATAATC
          TTTATGTTTC CAAGAACTCC CAACACAATT TAACTTTCGC TCTTTATTAG
                      Repeat Region
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1651      ATAAATTATT TCATTATCGC GATATCCGTT AAGTTTGTAT CGTAATCTGC
          TATTTAATAA AGTAATAGCG CTATAGGCAA TTCAAACATA GCATTAGACG
                      Repeat Region
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1701      AGCCCCCACC ATGGATCTGG TGCTAAAAAG ATGCCTTCTT CATTTGGCTG
          TCGGGGGTGG TACCTAGACC ACGATTTTTC TACGGAAGAA GTAAACCGAC
                      Repeat Region
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1751      TGATAGGTGC TTTGCTGGCT GTGGGGGCTA CAAAAGTACC CAGAAACCAG
          ACTATCCACG AAACGACCGA CACCCCCGAT GTTTTCATGG GTCTTTGGTC
                      Repeat Region
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1801      GACTGGCTTG GTGTCTCAAG GCAACTCAGA ACCAAAGCCT GGAACAGGCA
          CTGACCGAAC CACAGAGTTC CGTTGAGTCT TGGTTTCGGA CCTTGTCCGT
                      Repeat Region
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1851      GCTGTATCCA GAGTGGACAG AAGCCCAGAG ACTTGACTGC TGGAGAGGTG
          CGACATAGGT CTCACCTGTC TTCGGGTCTC TGAACTGACG ACCTCTCCAC
                      Repeat Region
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1901      GTCAAGTGTC CCTCAAGGTC AGTAATGATG GGCCTACACT GATTGGTGCA
          CAGTTCACAG GGAGTTCCAG TCATTACTAC CCGGATGTGA CTAACCACGT
                      Repeat Region
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1951      AATGCCTCCT TCTCTATTGC CTTGAACTTC CCTGGAAGCC AAAAGGTATT
          TTACGGAGGA AGAGATAACG GAACTTGAAG GGACCTTCGG TTTTCCATAA
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          Repeat Region                      C1B promoter
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     2001 GCCAGATACT AGTTCTAGAG GATCATTATT TAACGTAAAC TAAATGGAAA
          CGGTCTATGA TCAAGATCTC CTAGTAATAA ATTGCATTTG ATTTACCTTT
                                C1B promoter
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2051 AGCTATTTAC AGGTACATAC GGTGTTTTTC TGGAATCAAA TGATTCTGAT
          TCGATAAATG TCCATGTATG CCACAAAAAG ACCTTAGTTT ACTAAGACTA
                                C1B promoter
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2101 TTTGAGGATT TTATCAATAC AATAATGACA GTGCTAACTG GTAAAAAAGA
          AAACTCCTAA AATAGTTATG TTATTACTGT CACGATTGAC CATTTTTTCT
                                C1B promoter
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2151 AAGCAAACAA TTATCATGGC TAACAATTTT TATTATATTT GTAGTATGCA
          TTCGTTTGTT AATAGTACCG ATTGTTAAAA ATAATATAAA CATCATACGT
                                C1B promoter
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2201 TAGTGGTCTT TACGTTTCTT TATTTAAAGT TAATGTGTTA AGATTAAATG
          ATCACCAGAA ATGCAAAGAA ATAAATTTCA ATTACACAAT TCTAATTTAC
          C1B promoter                        LacZ
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     2251 GAGTAATTGG ATCCCCCATC GATGGGGAAT TCACTGGCCG TCGTTTTACA
          CTCATTAACC TAGGGGGTAG CTACCCCTTA AGTGACCGGC AGCAAAATGT
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2301 ACGTCGTGAC TGGGAAAACC CTGGCGTTAC CCAACTTAAT CGCCTTGCAG
          TGCAGCACTG ACCCTTTTGG GACCGCAATG GGTTGAATTA GCGGAACGTC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2351 CACATCCCCC TTTCGCCAGC TGGCGTAATA GCGAAGAGGC CCGCACCGAT
          GTGTAGGGGG AAAGCGGTCG ACCGCATTAT CGCTTCTCCG GGCGTGGCTA
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2401 CGCCCTTCCC AACAGTTGCG CAGCCTGAAT GGCGAATGGC GCTTTGCCTG
          GCGGGAAGGG TTGTCAACGC GTCGGACTTA CCGCTTACCG CGAAACGGAC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2451 GTTTCCGGCA CCAGAAGCGG TGCCGGAAAG CTGGCTGGAG TGCGATCTTC
          CAAAGGCCGT GGTCTTCGCC ACGGCCTTTC GACCGACCTC ACGCTAGAAG
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2501 CTGAGGCCGA TACTGTCGTC GTCCCCTCAA ACTGGCAGAT GCACGGTTAC
          GACTCCGGCT ATGACAGCAG CAGGGGAGTT TGACCGTCTA CGTGCCAATG
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2551 GATGCGCCCA TCTACACCAA CGTGACCTAT CCCATTACGG TCAATCCGCC
          CTACGCGGGT AGATGTGGTT GCACTGGATA GGGTAATGCC AGTTAGGCGG
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2601 GTTTGTTCCC ACGGAGAATC CGACGGGTTG TTACTCGCTC ACATTTAATG
          CAAACAAGGG TGCCTCTTAG GCTGCCCAAC AATGAGCGAG TGTAAATTAC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
     2651 TTGATGAAAG CTGGCTACAG GAAGGCCAGA CGCGAATTAT TTTTGATGGC
          AACTACTTTC GACCGATGTC CTTCCGGTCT GCGCTTAATA AAAACTACCG
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                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2701     GTTAACTCGG CGTTTCATCT GTGGTGCAAC GGGCGCTGGG TCGGTTACGG
         CAATTGAGCC GCAAAGTAGA CACCACGTTG CCCGCGACCC AGCCAATGCC
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2751     CCAGGACAGT CGTTTGCCGT CTGAATTTGA CCTGAGCGCA TTTTTACGCG
         GGTCCTGTCA GCAAACGGCA GACTTAAACT GGACTCGCGT AAAAATGCGC
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2801     CCGGAGAAAA CCGCCTCGCG GTGATGGTGC TGCGCTGGAG TGACGGCAGT
         GGCCTCTTTT GGCGGAGCGC CACTACCACG ACGCGACCTC ACTGCCGTCA
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2851     TATCTGGAAG ATCAGGATAT GTGGCGGATG AGCGGCATTT TCCGTGACGT
         ATAGACCTTC TAGTCCTATA CACCGCCTAC TCGCCGTAAA AGGCACTGCA
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2901     CTCGTTGCTG CATAAACCGA CTACACAAAT CAGCGATTTC CATGTTGCCA
         GAGCAACGAC GTATTTGGCT GATGTGTTTA GTCGCTAAAG GTACAACGGT
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2951     CTCGCTTTAA TGATGATTTC AGCCGCGCTG TACTGGAGGC TGAAGTTCAG
         GAGCGAAATT ACTACTAAAG TCGGCGCGAC ATGACCTCCG ACTTCAAGTC
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3001     ATGTGCGGCG AGTTGCGTGA CTACCTACGG GTAACAGTTT CTTTATGGCA
         TACACGCCGC TCAACGCACT GATGGATGCC CATTGTCAAA GAAATACCGT
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3051     GGGTGAAACG CAGGTCGCCA GCGGCACCGC GCCTTTCGGC GGTGAAATTA
         CCCACTTTGC GTCCAGCGGT CGCCGTGGCG CGGAAAGCCG CCACTTTAAT
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3101     TCGATGAGCG TGGTGGTTAT GCCGATCGCG TCACACTACG TCTGAACGTC
         AGCTACTCGC ACCACCAATA CGGCTAGCGC AGTGTGATGC AGACTTGCAG
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3151     GAAAACCCGA AACTGTGGAG CGCCGAAATC CCGAATCTCT ATCGTGCGGT
         CTTTTGGGCT TTGACACCTC GCGGCTTTAG GGCTTAGAGA TAGCACGCCA
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3201     GGTTGAACTG CACACCGCCG ACGGCACGCT GATTGAAGCA GAAGCCTGCG
         CCAACTTGAC GTGTGGCGGC TGCCGTGCGA CTAACTTCGT CTTCGGACGC
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3251     ATGTCGGTTT CCGCGAGGTG CGGATTGAAA ATGGTCTGCT GCTGCTGAAC
         TACAGCCAAA GGCGCTCCAC GCCTAACTTT TACCAGACGA CGACGACTTG
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3301     GGCAAGCCGT TGCTGATTCG AGGCGTTAAC CGTCACGAGC ATCATCCTCT
         CCGTTCGGCA ACGACTAAGC TCCGCAATTG GCAGTGCTCG TAGTAGGAGA
                                 LacZ
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3351     GCATGGTCAG GTCATGGATG AGCAGACGAT GGTGCAGGAT ATCCTGCTGA
         CGTACCAGTC CAGTACCTAC TCGTCTGCTA CCACGTCCTA TAGGACGACT
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                                   LacZ
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   3401   TGAAGCAGAA CAACTTTAAC GCCGTGCGCT GTTCGCATTA TCCGAACCAT
          ACTTCGTCTT GTTGAAATTG CGGCACGCGA CAAGCGTAAT AGGCTTGGTA
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   3451   CCGCTGTGGT ACACGCTGTG CGACCGCTAC GGCCTGTATG TGGTGGATGA
          GGCGACACCA TGTGCGACAC GCTGGCGATG CCGGACATAC ACCACCTACT
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   3501   AGCCAATATT GAAACCCACG GCATGGTGCC AATGAATCGT CTGACCGATG
          TCGGTTATAA CTTTGGGTGC CGTACCACGG TTACTTAGCA GACTGGCTAC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   3551   ATCCGCGCTG GCTACCGGCG ATGAGCGAAC GCGTAACGCG AATGGTGCAG
          TAGGCGCGAC CGATGGCCGC TACTCGCTTG CGCATTGCGC TTACCACGTC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   3601   CGCGATCGTA ATCACCCGAG TGTGATCATC TGGTCGCTGG GGAATGAATC
          GCGCTAGCAT TAGTGGGCTC ACACTAGTAG ACCAGCGACC CCTTACTTAG
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   3651   AGGCCACGGC GCTAATCACG ACGCGCTGTA TCGCTGGATC AAATCTGTCG
          TCCGGTGCCG CGATTAGTGC TGCGCGACAT AGCGACCTAG TTTAGACAGC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   3701   ATCCTTCCCG CCCGGTGCAG TATGAAGGCG GCGGAGCCGA CACCACGGCC
          TAGGAAGGGC GGGCCACGTC ATACTTCCGC CGCCTCGGCT GTGGTGCCGG
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   3751   ACCGATATTA TTTGCCCGAT GTACGCGCGC GTGGATGAAG ACCAGCCCTT
          TGGCTATAAT AAACGGGCTA CATGCGCGCG CACCTACTTC TGGTCGGGAA
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   3801   CCCGGCTGTG CCGAAATGGT CCATCAAAAA ATGGCTTTCG CTACCTGGAG
          GGGCCGACAC GGCTTTACCA GGTAGTTTTT TACCGAAAGC GATGGACCTC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   3851   AGACGCGCCC GCTGATCCTT TGCGAATACG CCCACGCGAT GGGTAACAGT
          TCTGCGCGGG CGACTAGGAA ACGCTTATGC GGGTGCGCTA CCCATTGTCA
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   3901   CTTGGCGGTT TCGCTAAATA CTGGCAGGCG TTTCGTCAGT ATCCCCGTTT
          GAACCGCCAA AGCGATTTAT GACCGTCCGC AAAGCAGTCA TAGGGGCAAA
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   3951   ACAGGGCGGC TTCGTCTGGG ACTGGGTGGA TCAGTCGCTG ATTAAATATG
          TGTCCCGCCG AAGCAGACCC TGACCCACCT AGTCAGCGAC TAATTTATAC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   4001   ATGAAAACGG CAACCCGTGG TCGGCTTACG GCGGTGATTT TGGCGATACG
          TACTTTTGCC GTTGGGCACC AGCCGAATGC CGCCACTAAA ACCGCTATGC
                                   LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   4051   CCGAACGATC GCCAGTTCTG TATGAACGGT CTGGTCTTTG CCGACCGCAC
          GGCTTGCTAG CGGTCAAGAC ATACTTGCCA GACCAGAAAC GGCTGGCGTG
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                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4101  GCCGCATCCA GCGCTGACGG AAGCAAAACA CCAGCAGCAG TTTTTCCAGT
          CGGCGTAGGT CGCGACTGCC TTCGTTTTGT GGTCGTCGTC AAAAAGGTCA
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4151  TCCGTTTATC CGGGCAAACC ATCGAAGTGA CCAGCGAATA CCTGTTCCGT
          AGGCAAATAG GCCCGTTTGG TAGCTTCACT GGTCGCTTAT GGACAAGGCA
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4201  CATAGCGATA ACGAGCTCCT GCACTGGATG GTGGCGCTGG ATGGTAAGCC
          GTATCGCTAT TGCTCGAGGA CGTGACCTAC CACCGCGACC TACCATTCGG
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4251  GCTGGCAAGC GGTGAAGTGC CTCTGGATGT CGCTCCACAA GGTAAACAGT
          CGACCGTTCG CCACTTCACG GAGACCTACA GCGAGGTGTT CCATTTGTCA
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4301  TGATTGAACT GCCTGAACTA CCGCAGCCGG AGAGCGCCGG GCAACTCTGG
          ACTAACTTGA CGGACTTGAT GGCGTCGGCC TCTCGCGGCC CGTTGAGACC
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4351  CTCACAGTAC GCGTAGTGCA ACCGAACGCG ACCGCATGGT CAGAAGCCGG
          GAGTGTCATG CGCATCACGT TGGCTTGCGC TGGCGTACCA GTCTTCGGCC
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4401  GCACATCAGC GCCTGGCAGC AGTGGCGTCT GGCGGAAAAC CTCAGTGTGA
          CGTGTAGTCG CGGACCGTCG TCACCGCAGA CCGCCTTTTG GAGTCACACT
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4451  CGCTCCCCGC CGCGTCCCAC GCCATCCCGC ATCTGACCAC CAGCGAAATG
          GCGAGGGGCG GCGCAGGGTG CGGTAGGGCG TAGACTGGTG GTCGCTTTAC
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4501  GATTTTTGCA TCGAGCTGGG TAATAAGCGT TGGCAATTTA ACCGCCAGTC
          CTAAAAACGT AGCTCGACCC ATTATTCGCA ACCGTTAAAT TGGCGGTCAG
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4551  AGGCTTTCTT TCACAGATGT GGATTGGCGA TAAAAAACAA CTGCTGACGC
          TCCGAAAGAA AGTGTCTACA CCTAACCGCT ATTTTTTGTT GACGACTGCG
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4601  CGCTGCGCGA TCAGTTCACC CGTGCACCGC TGGATAACGA CATTGGCGTA
          GCGACGCGCT AGTCAAGTGG GCACGTGGCG ACCTATTGCT GTAACCGCAT
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4651  AGTGAAGCGA CCCGCATTGA CCCTAACGCC TGGGTCGAAC GCTGGAAGGC
          TCACTTCGCT GGGCGTAACT GGGATTGCGG ACCCAGCTTG CGACCTTCCG
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4701  GGCGGGCCAT TACCAGGCCG AAGCAGCGTT GTTGCAGTGC ACGGCAGATA
          CCGCCCGGTA ATGGTCCGGC TTCGTCGCAA CAACGTCACG TGCCGTCTAT
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    4751  CACTTGCTGA TGCGGTGCTG ATTACGACCG CTCACGCGTG GCAGCATCAG
          GTGAACGACT ACGCCACGAC TAATGCTGGC GAGTGCGCAC CGTCGTAGTC
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                              LacZ
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   4801   GGGAAAACCT TATTTATCAG CCGGAAAACC TACCGGATTG ATGGTAGTGG
          CCCTTTTGGA ATAAATAGTC GGCCTTTTGG ATGGCCTAAC TACCATCACC
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   4851   TCAAATGGCG ATTACCGTTG ATGTTGAAGT GGCGAGCGAT ACACCGCATC
          AGTTTACCGC TAATGGCAAC TACAACTTCA CCGCTCGCTA TGTGGCGTAG
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   4901   CGGCGCGGAT TGGCCTGAAC TGCCAGCTGG CGCAGGTAGC AGAGCGGGTA
          GCCGCGCCTA ACCGGACTTG ACGGTCGACC GCGTCCATCG TCTCGCCCAT
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   4951   AACTGGCTCG GATTAGGGCC GCAAGAAAAC TATCCCGACC GCCTTACTGC
          TTGACCGAGC CTAATCCCGG CGTTCTTTTG ATAGGGCTGG CGGAATGACG
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   5001   CGCCTGTTTT GACCGCTGGG ATCTGCCATT GTCAGACATG TATACCCCGT
          GCGGACAAAA CTGGCGACCC TAGACGGTAA CAGTCTGTAC ATATGGGGCA
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   5051   ACGTCTTCCC GAGCGAAAAC GGTCTGCGCT GCGGGACGCG CGAATTGAAT
          TGCAGAAGGG CTCGCTTTTG CCAGACGCGA CGCCCTGCGC GCTTAACTTA
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   5101   TATGGCCCAC ACCAGTGGCG CGGCGACTTC CAGTTCAACA TCAGCCGGTA
          ATACCGGGTG TGGTCACCGC GCCGCTGAAG GTCAAGTTGT AGTCGGCCAT
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   5151   CAGTCAACAG CAATTGATGG AAACCAGCCA TTCGCCATCT GCTGCACGCG
          GTCAGTTGTC GTTAACTACC TTTGGTCGGT AAGCGGTAGA CGACGTGCGC
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   5201   GAAGAGGCAC ATGGCTGAAT ATCGACGGTT TCCATATGGG GATTGGTGGC
          CTTCTCCGTG TACCGACTTA TAGCTGCCAA AGGTATACCC CTAACCACCG
                              LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   5251   GACGACTCCT GGAGCCCGTC AGTATCGGCG GAATTCCAGC TGAGCGCCGG
          CTGCTGAGGA CCTCGGGCAG TCATAGCCGC CTTAAGGTCG ACTCGCGGCC
                       LacZ
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   5301   TCGCTACCAT TACCAGTTGG TCTGGTGTCA AAAATAATAA TAACCGGGCA
          AGCGATGGTA ATGGTCAACC AGACCACAGT TTTTATTATT ATTGGCCCGT
   5351   GGGGGGATCC GGAGCTTATC GCAGATCAAT TCGATATCAA GCTTATCGAT
          CCCCCCTAGG CCTCGAATAG CGTCTAGTTA AGCTATAGTT CGAATAGCTA
                                                H6  Promoter
                                              ~~~~~~~~~~~~~~~~~
   5401   ACCGTCGACC TCGAGTCTAG AATCGATCCC GGGTTCTTTA TTCTATACTT
          TGGCAGCTGG AGCTCAGATC TTAGCTAGGG CCCAAGAAAT AAGATATGAA
                          H6  Promoter
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   5451   AAAAAGTGAA AATAAATACA AAGGTTCTTG AGGGTTGTGT TAAATTGAAA
          TTTTTCACTT TTATTTATGT TTCCAAGAAC TCCCAACACA ATTTAACTTT
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      H6  Promoter
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5501  GCGAGAAATA ATCATAAATT ATTTCATTAT CGCGATATCC GTTAAGTTTG
      CGCTCTTTAT TAGTATTTAA TAAAGTAATA GCGCTATAGG CAATTCAAAC
      H6  Promoter                         gp100(M)
      ~~~~~~~                     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5551  TATCGTAATC TGCAGCCCCC ACCATGGATC TGGTGCTAAA AAGATGCCTT
      ATAGCATTAG ACGTCGGGGG TGGTACCTAG ACCACGATTT TTCTACGGAA
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5601  CTTCATTTGG CTGTGATAGG TGCTTTGCTG GCTGTGGGGG CTACAAAAGT
      GAAGTAAACC GACACTATCC ACGAAACGAC CGACACCCCC GATGTTTTCA
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5651  ACCCAGAAAC CAGGACTGGC TTGGTGTCTC AAGGCAACTC AGAACCAAAG
      TGGGTCTTTG GTCCTGACCG AACCACAGAG TTCCGTTGAG TCTTGGTTTC
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5701  CCTGGAACAG GCAGCTGTAT CCAGAGTGGA CAGAAGCCCA GAGACTTGAC
      GGACCTTGTC CGTCGACATA GGTCTCACCT GTCTTCGGGT CTCTGAACTG
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5751  TGCTGGAGAG GTGGTCAAGT GTCCCTCAAG GTCAGTAATG ATGGGCCTAC
      ACGACCTCTC CACCAGTTCA CAGGGAGTTC CAGTCATTAC TACCCGGATG
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5801  ACTGATTGGT GCAAATGCCT CCTTCTCTAT TGCCTTGAAC TTCCCTGGAA
      TGACTAACCA CGTTTACGGA GGAAGAGATA ACGGAACTTG AAGGGACCTT
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5851  GCCAAAAGGT ATTGCCAGAT GGGCAGGTTA TCTGGGTCAA CAATACCATC
      CGGTTTTCCA TAACGGTCTA CCCGTCCAAT AGACCCAGTT GTTATGGTAG
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5901  ATCAATGGGA GCCAGGTGTG GGGAGGACAG CCAGTGTATC CCCAGGAAAC
      TAGTTACCCT CGGTCCACAC CCCTCCTGTC GGTCACATAG GGGTCCTTTG
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5951  TGACGATGCC TGCATCTTCC CTGATGGTGG ACCTTGCCCA TCTGGCTCTT
      ACTGCTACGG ACGTAGAAGG GACTACCACC TGGAACGGGT AGACCGAGAA
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6001  GGTCTCAGAA GAGAAGCTTT GTTTATGTCT GGAAGACCTG GGGCCAATAC
      CCAGAGTCTT CTCTTCGAAA CAAATACAGA CCTTCTGGAC CCCGGTTATG
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6051  TGGCAAGTTC TAGGGGGCCC AGTGTCTGGG CTGAGCATTG GGACAGGCAG
      ACCGTTCAAG ATCCCCCGGG TCACAGACCC GACTCGTAAC CCTGTCCGTC
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6101  GGCAATGCTG GGCACACACA CGATGGAAGT GACTGTCTAC CATCGCCGGG
      CCGTTACGAC CCGTGTGTGT GCTACCTTCA CTGACAGATG GTAGCGGCCC
                            gp100(M)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6151  GATCCCGGAG CTATGTGCCT CTTGCTCATT CCAGCTCAGC CTTCACCATT
      CTAGGGCCTC GATACACGGA GAACGAGTAA GGTCGAGTCG GAAGTGGTAA
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                     gp100(M)
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6201 ATGGACCAGG TGCCTTTCTC CGTGAGCGTG TCCCAGTTGC GGGCCTTGGA
     TACCTGGTCC ACGGAAAGAG GCACTCGCAC AGGGTCAACG CCCGGAACCT
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6251 TGGAGGGAAC AAGCACTTCC TGAGAAATCA GCCTCTGACC TTTGCCCTCC
     ACCTCCCTTG TTCGTGAAGG ACTCTTTAGT CGGAGACTGG AAACGGGAGG
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6301 AGCTCCATGA CCCCAGTGGC TATCTGGCTG AAGCTGACCT CTCCTACACC
     TCGAGGTACT GGGGTCACCG ATAGACCGAC TTCGACTGGA GAGGATGTGG
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6351 TGGGACTTTG GAGACAGTAG TGGAACCCTG ATCTCTCGGG CACTTGTGGT
     ACCCTGAAAC CTCTGTCATC ACCTTGGGAC TAGAGAGCCC GTGAACACCA
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6401 CACTCATACT TACCTGGAGC CTGGCCCAGT CACTGTTCAG GTGGTCCTGC
     GTGAGTATGA ATGGACCTCG GACCGGGTCA GTGACAAGTC CACCAGGACG
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6451 AGGCTGCCAT TCCTCTCACC TCCTGTGGCT CCTCCCCAGT TCCAGGCACC
     TCCGACGGTA AGGAGAGTGG AGGACACCGA GGAGGGGTCA AGGTCCGTGG
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6501 ACAGATGGGC ACAGGCCAAC TGCAGAGGCC CCTAACACCA CAGCTGGCCA
     TGTCTACCCG TGTCCGGTTG ACGTCTCCGG GGATTGTGGT GTCGACCGGT
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6551 AGTGCCTACT ACAGAAGTTG TGGGTACTAC ACCTGGTCAG GCGCCAACTG
     TCACGGATGA TGTCTTCAAC ACCCATGATG TGGACCAGTC CGCGGTTGAC
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6601 CAGAGCCCTC TGGAACCACA TCTGTGCAGG TGCCAACCAC TGAAGTCATA
     GTCTCGGGAG ACCTTGGTGT AGACACGTCC ACGGTTGGTG ACTTCAGTAT
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6651 AGCACTGCAC CTGTGCAGAT GCCAACTGCA GAGAGCACAG GTATGACACC
     TCGTGACGTG GACACGTCTA CGGTTGACGT CTCTCGTGTC CATACTGTGG
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6701 TGAGAAGGTG CCAGTTTCAG AGGTCATGGG TACCACACTG GCAGAGATGT
     ACTCTTCCAC GGTCAAAGTC TCCAGTACCC ATGGTGTGAC CGTCTCTACA
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6751 CAACTCCAGA GGCTACAGGT ATGACACCTG CAGAGGTATC AATTGTGGTG
     GTTGAGGTCT CCGATGTCCA TACTGTGGAC GTCTCCATAG TTAACACCAC
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6801 CTTTCTGGAA CCACAGCTGC ACAGGTAACA ACTACAGAGT GGGTGGAGAC
     GAAAGACCTT GGTGTCGACG TGTCCATTGT TGATGTCTCA CCCACCTCTG
                     gp100(M)
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
6851 CACAGCTAGA GAGCTACCTA TCCCTGAGCC TGAAGGTCCA GATGCCAGCT
     GTGTCGATCT CTCGATGGAT AGGGACTCGG ACTTCCAGGT CTACGGTCGA
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                              gp100(M)
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 6901  CAATCATGTC TACGGAAAGT ATTACAGGTT CCCTGGGCCC CCTGCTGGAT
       GTTAGTACAG ATGCCTTTCA TAATGTCCAA GGGACCCGGG GGACGACCTA
                              gp100(M)
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 6951  GGTACAGCCA CCTTAAGGCT GGTGAAGAGA CAAGTCCCCC TGGATTGTGT
       CCATGTCGGT GGAATTCCGA CCACTTCTCT GTTCAGGGGG ACCTAACACA
                              gp100(M)
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 7001  TCTGTATCGA TATGGTTCCT TTTCCGTCAC CCTGGACATT GTCCAGGGTA
       AGACATAGCT ATACCAAGGA AAAGGCAGTG GGACCTGTAA CAGGTCCCAT
                              gp100(M)
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 7051  TTGAAAGTGC CGAGATCCTG CAGGCTGTGC CGTCCGGTGA GGGGGATGCA
       AACTTTCACG GCTCTAGGAC GTCCGACACG GCAGGCCACT CCCCCTACGT
                              gp100(M)
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 7101  TTTGAGCTGA CTGTGTCCTG CCAAGGCGGG CTGCCCAAGG AAGCCTGCAT
       AAACTCGACT GACACAGGAC GGTTCCGCCC GACGGGTTCC TTCGGACGTA
                              gp100(M)
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 7151  GGAGATCTCA TCGCCAGGGT GCCAGCCCCC TGCCCAGCGG CTGTGCCAGC
       CCTCTAGAGT AGCGGTCCCA CGGTCGGGGG ACGGGTCGCC GACACGGTCG
                              gp100(M)
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 7201  CTGTGCTACC CAGCCCAGCC TGCCAGCTGG TTCTGCACCA GATACTGAAG
       GACACGATGG GTCGGGTCGG ACGGTCGACC AAGACGTGGT CTATGACTTC
                              gp100(M)
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 7251  GGTGGCTCGG GGACATACTG CCTCAATGTG TCTCTGGCTG ATACCAACAG
       CCACCGAGCC CCTGTATGAC GGAGTTACAC AGAGACCGAC TATGGTTGTC
                              gp100(M)
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 7301  CCTGGCAGTG GTCAGCACCC AGCTTATCAT GCCTGGTCAA GAAGCAGGCC
       GGACCGTCAC CAGTCGTGGG TCGAATAGTA CGGACCAGTT CTTCGTCCGG
                              gp100(M)
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 7351  TTGGGCAGGT TCCGCTGATC GTGGGCATCT TGCTGGTGTT GATGGCTGTG
       AACCCGTCCA AGGCGACTAG CACCCGTAGA ACGACCACAA CTACCGACAC
                              gp100(M)
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 7401  GTCCTTGCAT CTCTGATATA TAGGCGCAGA CTTATGAAGC AAGACTTCTC
       CAGGAACGTA GAGACTATAT ATCCGCGTCT GAATACTTCG TTCTGAAGAG
                              gp100(M)
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 7451  CGTACCCCAG TTGCCACATA GCAGCAGTCA CTGGCTGCGT CTACCCCGCA
       GCATGGGGTC AACGGTGTAT CGTCGTCAGT GACCGACGCA GATGGGGCGT
                              gp100(M)
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 7501  TCTTCTGCTC TTGTCCCATT GGTGAGAACA GCCCCCTCCT CAGTGGGCAG
       AGAAGACGAG AACAGGGTAA CCACTCTTGT CGGGGGAGGA GTCACCCGTC
       gp100(M)                         42K promoter
       ~~~~~~~~~            ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 7551  CAGGTCTGAT TTTTATTCTA GTTCAAAAAA ATATAAATGA TTCACCATCT
       GTCCAGACTA AAAATAAGAT CAAGTTTTTT TATATTTACT AAGTGGTAGA
```

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                        42K promoter
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7601  GATAGAAAAA AAATTTATTG GGAGAATATG ATAATATTTT GGGATTTCAA
      CTATCTTTTT TTTAAATAAC CCTCTTATAC TATTATAAAA CCCTAAAGTT
           42K promoter                          Mart-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~           ~~~~~~~~~~~~
7651  AATTGAAAAT ATATAATTAC AATATAAATC TAGACCACCA TGCCAAGAGA
      TTAACTTTTA TATATTAATG TTATATTTAG ATCTGGTGGT ACGGTTCTCT
                            Mart-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7701  AGATGCTCAC TTCATCTATG GTTACCCCAA GAAGGGGCAC GGCCACTCTT
      TCTACGAGTG AAGTAGATAC CAATGGGGTT CTTCCCCGTG CCGGTGAGAA
                            Mart-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7751  ACACCACGGC TGAAGAGGCC GCTGGGATCG GCATCCTGAC AGTGATCCTG
      TGTGGTGCCG ACTTCTCCGG CGACCCTAGC CGTAGGACTG TCACTAGGAC
                            Mart-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7801  GGAGTCTTAC TGCTCATCGG CTGTTGGTAT TGTAGAAGAC GAAATGGATA
      CCTCAGAATG ACGAGTAGCC GACAACCATA ACATCTTCTG CTTTACCTAT
                            Mart-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7851  CAGAGCCTTG ATGGATAAAA GTCTTCATGT TGGCACTCAA TGTGCCTTAA
      GTCTCGGAAC TACCTATTTT CAGAAGTACA ACCGTGAGTT ACACGGAATT
                            Mart-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7901  CAAGAAGATG CCCACAAGAA GGGTTTGATC ATCGGGACAG CAAAGTGTCT
      GTTCTTCTAC GGGTGTTCTT CCCAAACTAG TAGCCCTGTC GTTTCACAGA
                            Mart-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7951  CTTCAAGAGA AAAACTGTGA ACCTGTGGTT CCCAATGCTC CACCTGCTTA
      GAAGTTCTCT TTTTGACACT TGGACACCAA GGGTTACGAG GTGGACGAAT
                          Mart-1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8001  TGAGAAACTC TCTGCAGAAC AGTCACCACC ACCTTATTCA CCTTAATCTA
      ACTCTTTGAG AGACGTCTTG TCAGTGGTGG TGGAATAAGT GGAATTAGAT
                                  sE/L Promoter
                            ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8051  GAGTCGACCT GCAGGCATGC AAAAATTGAA ATTTTATTTT TTTTTTTTGG
      CTCAGCTGGA CGTCCGTACG TTTTTAACTT TAAAATAAAA AAAAAAAACC
      sE/L Promoter
      ~~~~~~~~~~~
                            Mage 1-3 minigene
                 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8101  AATATAAATA ATGGAGTCCT TGCAGCTGGT CTTTGGCATT GACGTGAAGG
      TTATATTTAT TACCTCAGGA ACGTCGACCA GAAACCGTAA CTGCACTTCC
                      Mage 1-3 minigene
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8151  AAGCAGACCC CACCGGCCAC TCCTATGTCC TTGTCACCTG CCTAGGTCTC
      TTCGTCTGGG GTGGCCGGTG AGGATACAGG AACAGTGGAC GGATCCAGAG
                      Mage 1-3 minigene
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8201  TCCTATGATG GCAATAAGCG TAAAGAAGTG GACCCCATCG GCCACTTGTA
      AGGATACTAC CGTTATTCGC ATTTCTTCAC CTGGGGTAGC CGGTGAACAT
```

```
     Mage 1-3 minigene                                   C5 Left Arm
       ~~~~                                                  ~~~~~~~
8251   CTAGTTTTTA TCCCGGGTTT TTATGACTAG TTAATCACGG CCGCTTATAA
       GATCAAAAAT AGGGCCCAAA AATACTGATC AATTAGTGCC GGCGAATATT
                              C5 Left Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8301   AGATCTAAAA TGCATAATTT CTAAATAATG AAAAAAAAGT ACATCATGAG
       TCTAGATTTT ACGTATTAAA GATTTATTAC TTTTTTTTCA TGTAGTACTC
                              C5 Left Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8351   CAACGCGTTA GTATATTTTA CAATGGAGAT TAACGCTCTA TACCGTTCTA
       GTTGCGCAAT CATATAAAAT GTTACCTCTA ATTGCGAGAT ATGGCAAGAT
                              C5 Left Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8401   TGTTTATTGA TTCAGATGAT GTTTTAGAAA AGAAAGTTAT TGAATATGAA
       ACAAATAACT AAGTCTACTA CAAAATCTTT TCTTTCAATA ACTTATACTT
                              C5 Left Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8451   AACTTTAATG AAGATGAAGA TGACGACGAT GATTATTGTT GTAAATCTGT
       TTGAAATTAC TTCTACTTCT ACTGCTGCTA CTAATAACAA CATTTAGACA
                              C5 Left Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8501   TTTAGATGAA GAAGATGACG CGCTAAAGTA TACTATGGTT ACAAAGTATA
       AAATCTACTT CTTCTACTGC GCGATTTCAT ATGATACCAA TGTTTCATAT
                              C5 Left Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8551   AGTCTATACT ACTAATGGCG ACTTGTGCAA GAAGGTATAG TATAGTGAAA
       TCAGATATGA TGATTACCGC TGAACACGTT CTTCCATATC ATATCACTTT
                              C5 Left Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8601   ATGTTGTTAG ATTATGATTA TGAAAAACCA AATAAATCAG ATCCATATCT
       TACAACAATC TAATACTAAT ACTTTTTGGT TTATTTAGTC TAGGTATAGA
                              C5 Left Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8651   AAAGGTATCT CCTTTGCACA TAATTTCATC TATTCCTAGT TTAGAATACT
       TTTCCATAGA GGAAACGTGT ATTAAAGTAG ATAAGGATCA AATCTTATGA
                              C5 Left Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8701   TTTCATTATA TTTGTTTACA GCTGAAGACG AAAAAAATAT ATCGATAATA
       AAAGTAATAT AAACAAATGT CGACTTCTGC TTTTTTTATA TAGCTATTAT
                              C5 Left Arm
       ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8751   GAAGATTATG TTAACTCTGC TAATAAGATG AAATTGAATG AGTCTGTGAC
       CTTCTAATAC AATTGAGACG ATTATTCTAC TTTAACTTAC TCAGACACTG
       C5 Left Arm
       ~~~~~
8801   TGCAGCCAAG CTTGGCACTG GCCGTCGTTT TACAACGTCG TGACTGGGAA
       ACGTCGGTTC GAACCGTGAC CGGCAGCAAA ATGTTGCAGC ACTGACCCTT
8851   AACCCTGGCG TTACCCAACT TAATCGCCTT GCAGCACATC CCCCTTTCGC
       TTGGGACCGC AATGGGTTGA ATTAGCGGAA CGTCGTGTAG GGGGAAAGCG
8901   CAGCTGGCGT AATAGCGAAG AGGCCCGCAC CGATCGCCCT TCCCAACAGT
       GTCGACCGCA TTATCGCTTC TCCGGGCGTG GCTAGCGGGA AGGGTTGTCA
8951   TGCGCAGCCT GAATGGCGAA TGGCGCCTGA TGCGGTATTT TCTCCTTACG
       ACGCGTCGGA CTTACCGCTT ACCGCGGACT ACGCCATAAA AGAGGAATGC
9001   CATCTGTGCG GTATTTCACA CCGCATATGG TGCACTCTCA GTACAATCTG
       GTAGACACGC CATAAAGTGT GGCGTATACC ACGTGAGAGT CATGTTAGAC
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9051  CTCTGATGCC GCATAGTTAA GCCAGCCCCG ACACCCGCCA ACACCCGCTG
      GAGACTACGG CGTATCAATT CGGTCGGGGC TGTGGGCGGT TGTGGGCGAC
9101  ACGCGCCCTG ACGGGCTTGT CTGCTCCCGG CATCCGCTTA CAGACAAGCT
      TGCGCGGGAC TGCCCGAACA GACGAGGGCC GTAGGCGAAT GTCTGTTCGA
9151  GTGACCGTCT CCGGGAGCTG CATGTGTCAG AGGTTTTCAC CGTCATCACC
      CACTGGCAGA GGCCCTCGAC GTACACAGTC TCCAAAAGTG GCAGTAGTGG
9201  GAAACGCGCG AGACGAAAGG GCCTCGTGAT ACGCCTATTT TTATAGGTTA
      CTTTGCGCGC TCTGCTTTCC CGGAGCACTA TGCGGATAAA AATATCCAAT
9251  ATGTCATGAT AATAATGGTT TCTTAGACGT CAGGTGGCAC TTTTCGGGGA
      TACAGTACTA TTATTACCAA AGAATCTGCA GTCCACCGTG AAAAGCCCCT
9301  AATGTGCGCG GAACCCCTAT TTGTTTATTT TTCTAAATAC ATTCAAATAT
      TTACACGCGC CTTGGGGATA AACAAATAAA AAGATTTATG TAAGTTTATA
9351  GTATCCGCTC ATGAGACAAT AACCCTGATA AATGCTTCAA TAATATTGAA
      CATAGGCGAG TACTCTGTTA TTGGGACTAT TTACGAAGTT ATTATAACTT
                                    Amp(R)
                        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9401  AAAGGAAGAG TATGAGTATT CAACATTTCC GTGTCGCCCT TATTCCCTTT
      TTTCCTTCTC ATACTCATAA GTTGTAAAGG CACAGCGGGA ATAAGGGAAA
                               Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9451  TTTGCGGCAT TTTGCCTTCC TGTTTTTGCT CACCCAGAAA CGCTGGTGAA
      AAACGCCGTA AAACGGAAGG ACAAAAACGA GTGGGTCTTT GCGACCACTT
                               Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9501  AGTAAAAGAT GCTGAAGATC AGTTGGGTGC ACGAGTGGGT TACATCGAAC
      TCATTTTCTA CGACTTCTAG TCAACCCACG TGCTCACCCA ATGTAGCTTG
                               Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9551  TGGATCTCAA CAGCGGTAAG ATCCTTGAGA GTTTTCGCCC CGAAGAACGT
      ACCTAGAGTT GTCGCCATTC TAGGAACTCT CAAAAGCGGG GCTTCTTGCA
                               Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9601  TTTCCAATGA TGAGCACTTT TAAAGTTCTG CTATGTGGCG CGGTATTATC
      AAAGGTTACT ACTCGTGAAA ATTTCAAGAC GATACACCGC GCCATAATAG
                               Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9651  CCGTATTGAC GCCGGGCAAG AGCAACTCGG TCGCCGCATA CACTATTCTC
      GGCATAACTG CGGCCCGTTC TCGTTGAGCC AGCGGCGTAT GTGATAAGAG
                               Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9701  AGAATGACTT GGTTGAGTAC TCACCAGTCA CAGAAAAGCA TCTTACGGAT
      TCTTACTGAA CCAACTCATG AGTGGTCAGT GTCTTTTCGT AGAATGCCTA
                               Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9751  GGCATGACAG TAAGAGAATT ATGCAGTGCT GCCATAACCA TGAGTGATAA
      CCGTACTGTC ATTCTCTTAA TACGTCACGA CGGTATTGGT ACTCACTATT
                               Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9801  CACTGCGGCC AACTTACTTC TGACAACGAT CGGAGGACCG AAGGAGCTAA
      GTGACGCCGG TTGAATGAAG ACTGTTGCTA GCCTCCTGGC TTCCTCGATT
                               Amp(R)
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9851  CCGCTTTTTT GCACAACATG GGGGATCATG TAACTCGCCT TGATCGTTGG
      GGCGAAAAAA CGTGTTGTAC CCCCTAGTAC ATTGAGCGGA ACTAGCAACC
```

```
                                Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 9901   GAACCGGAGC TGAATGAAGC CATACCAAAC GACGAGCGTG ACACCACGAT
        CTTGGCCTCG ACTTACTTCG GTATGGTTTG CTGCTCGCAC TGTGGTGCTA
                                Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 9951   GCCTGTAGCA ATGGCAACAA CGTTGCGCAA ACTATTAACT GGCGAACTAC
        CGGACATCGT TACCGTTGTT GCAACGCGTT TGATAATTGA CCGCTTGATG
                                Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
10001   TTACTCTAGC TTCCCGGCAA CAATTAATAG ACTGGATGGA GGCGGATAAA
        AATGAGATCG AAGGGCCGTT GTTAATTATC TGACCTACCT CCGCCTATTT
                                Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
10051   GTTGCAGGAC CACTTCTGCG CTCGGCCCTT CCGGCTGGCT GGTTTATTGC
        CAACGTCCTG GTGAAGACGC GAGCCGGGAA GGCCGACCGA CCAAATAACG
                                Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
10101   TGATAAATCT GGAGCCGGTG AGCGTGGGTC TCGCGGTATC ATTGCAGCAC
        ACTATTTAGA CCTCGGCCAC TCGCACCCAG AGCGCCATAG TAACGTCGTG
                                Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
10151   TGGGGCCAGA TGGTAAGCCC TCCCGTATCG TAGTTATCTA CACGACGGGG
        ACCCCGGTCT ACCATTCGGG AGGGCATAGC ATCAATAGAT GTGCTGCCCC
                                Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
10201   AGTCAGGCAA CTATGGATGA ACGAAATAGA CAGATCGCTG AGATAGGTGC
        TCAGTCCGTT GATACCTACT TGCTTTATCT GTCTAGCGAC TCTATCCACG
                Amp(R)
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~
10251   CTCACTGATT AAGCATTGGT AACTGTCAGA CCAAGTTTAC TCATATATAC
        GAGTGACTAA TTCGTAACCA TTGACAGTCT GGTTCAAATG AGTATATATG
10301   TTTAGATTGA TTTAAAACTT CATTTTTAAT TTAAAAGGAT CTAGGTGAAG
        AAATCTAACT AAATTTTGAA GTAAAAATTA AATTTTCCTA GATCCACTTC
10351   ATCCTTTTTG ATAATCTCAT GACCAAAATC CCTTAACGTG AGTTTTCGTT
        TAGGAAAAAC TATTAGAGTA CTGGTTTTAG GGAATTGCAC TCAAAAGCAA
10401   CCACTGAGCG TCAGACCCCG TAGAAAAGAT CAAAGGATCT TCTTGAGATC
        GGTGACTCGC AGTCTGGGGC ATCTTTTCTA GTTTCCTAGA AGAACTCTAG
10451   CTTTTTTTCT GCGCGTAATC TGCTGCTTGC AAACAAAAAA ACCACCGCTA
        GAAAAAAAGA CGCGCATTAG ACGACGAACG TTTGTTTTTT TGGTGGCGAT
10501   CCAGCGGTGG TTTGTTTGCC GGATCAAGAG CTACCAACTC TTTTTCCGAA
        GGTCGCCACC AAACAAACGG CCTAGTTCTC GATGGTTGAG AAAAAGGCTT
10551   GGTAACTGGC TTCAGCAGAG CGCAGATACC AAATACTGTC CTTCTAGTGT
        CCATTGACCG AAGTCGTCTC GCGTCTATGG TTTATGACAG GAAGATCACA
10601   AGCCGTAGTT AGGCCACCAC TTCAAGAACT CTGTAGCACC GCCTACATAC
        TCGGCATCAA TCCGGTGGTG AAGTTCTTGA GACATCGTGG CGGATGTATG
10651   CTCGCTCTGC TAATCCTGTT ACCAGTGGCT GCTGCCAGTG GCGATAAGTC
        GAGCGAGACG ATTAGGACAA TGGTCACCGA CGACGGTCAC CGCTATTCAG
10701   GTGTCTTACC GGGTTGGACT CAAGACGATA GTTACCGGAT AAGGCGCAGC
        CACAGAATGG CCCAACCTGA GTTCTGCTAT CAATGGCCTA TTCCGCGTCG
10751   GGTCGGGCTG AACGGGGGGT TCGTGCACAC AGCCCAGCTT GGAGCGAACG
        CCAGCCCGAC TTGCCCCCCA AGCACGTGTG TCGGGTCGAA CCTCGCTTGC
10801   ACCTACACCG AACTGAGATA CCTACAGCGT GAGCTATGAG AAAGCGCCAC
        TGGATGTGGC TTGACTCTAT GGATGTCGCA CTCGATACTC TTTCGCGGTG
10851   GCTTCCCGAA GGGAGAAAGG CGGACAGGTA TCCGGTAAGC GGCAGGGTCG
        CGAAGGGCTT CCCTCTTTCC GCCTGTCCAT AGGCCATTCG CCGTCCCAGC
```

```
10901  GAACAGGAGA GCGCACGAGG GAGCTTCCAG GGGGAAACGC CTGGTATCTT
       CTTGTCCTCT CGCGTGCTCC CTCGAAGGTC CCCCTTTGCG GACCATAGAA
10951  TATAGTCCTG TCGGGTTTCG CCACCTCTGA CTTGAGCGTC GATTTTTGTG
       ATATCAGGAC AGCCCAAAGC GGTGGAGACT GAACTCGCAG CTAAAAACAC
11001  ATGCTCGTCA GGGGGGCGGA GCCTATGGAA AAACGCCAGC AACGCGGCCT
       TACGAGCAGT CCCCCCGCCT CGGATACCTT TTTGCGGTCG TTGCGCCGGA
11051  TTTTACGGTT CCTGGCCTTT TGCTGGCCTT TTGCTCACAT GTTCTTTCCT
       AAAATGCCAA GGACCGGAAA ACGACCGGAA AACGAGTGTA CAAGAAAGGA
11101  GCGTTATCCC CTGATTCTGT GGATAACCGT ATTACCGCCT TTGAGTGAGC
       CGCAATAGGG GACTAAGACA CCTATTGGCA TAATGGCGGA AACTCACTCG
11151  TGATACCGCT CGCCGCAGCC GAACGACCGA GCGCAGCGAG TCAGTGAGCG
       ACTATGGCGA GCGGCGTCGG CTTGCTGGCT CGCGTCGCTC AGTCACTCGC
11201  AGGAAGCGGA AGAGCGCCCA ATACGCAAAC CGCCTCTCCC CGCGCGTTGG
       TCCTTCGCCT TCTCGCGGGT TATGCGTTTG GCGGAGAGGG GCGCGCAACC
11251  CCGATTCATT AATGCAGCTG GCACGACAGG TTTCCCGACT GGAAAGCGGG
       GGCTAAGTAA TTACGTCGAC CGTGCTGTCC AAAGGGCTGA CCTTTCGCCC
11301  CAGTGAGCGC AACGCAATTA ATGTGAGTTA GCTCACTCAT TAGGCACCCC
       GTCACTCGCG TTGCGTTAAT TACACTCAAT CGAGTGAGTA ATCCGTGGGG
11351  AGGCTTTACA CTTTATGCTT CCGGCTCGTA TGTTGTGTGG AATTGTGAGC
       TCCGAAATGT GAAATACGAA GGCCGAGCAT ACAACACACC TTAACACTCG
11401  GGATAACAAT TTCACACAGG AAACAGCTAT GACCATGATT ACGAATTGAA
       CCTATTGTTA AAGTGTGTCC TTTGTCGATA CTGGTACTAA TGCTTAACTT
11451  TTGCGGCCGC AATTCAACGC CGGCGTTAAG
```

FIGURE 6A

NY-ESO-1

Met Gln Ala Glu Gly Arg Gly Thr Gly Gly Ser Thr Gly Asp Ala Asp Gly Pro Gly Gly Pro Gly Ile Pro Asp Gly Pro Gly Gly Asn Ala Gly Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala Gly Ala Ala Arg Ala Ser Gly Pro Gly Gly Gly Ala Pro Arg Gly Pro His Gly Gly Ala Ala Ser Gly Leu Asn Gly Cys Cys Arg Cys Gly Ala Arg Gly Pro Glu Ser Arg Leu Leu Glu Phe Tyr Leu Ala Met Pro Phe Ala Thr Pro Met Glu Ala Glu Leu Ala Arg Arg Ser Leu Ala Gln Asp Ala Pro Pro Leu Pro Val Pro Gly Val Leu Leu Lys Glu Phe Thr Val Ser Gly Asn Ile Leu Thr Ile Arg Leu Thr Ala Ala Asp His Arg Gln Leu Gln Leu Ser Ile Ser Ser Cys Leu Gln Gln Leu Ser Leu Leu Met Trp Ile Thr Gln Cys Phe Leu Pro Val Phe Leu Ala Gln Pro Pro Ser Gly Gln Arg Arg

FIGURE 6C

TRP-2

Met Ser Pro Leu Trp Trp Gly Phe Leu Leu Ser Cys Leu Gly Cys Lys Ile Leu Pro Gly Ala Gln Gly Gln Phe Pro Arg Val Cys Met Thr Val Asp Ser Leu Val Asn Lys Glu Cys Cys Pro Arg Leu Gly Ala Glu Ser Ala Asn Val Cys Gly Ser Gln Gln Gly Arg Gly Gln Cys Thr Glu Val Arg Ala Asp Thr Arg Pro Trp Ser Gly Pro Tyr Ile Leu Arg Asn Gln Asp Asp Arg Glu Leu Trp Pro Arg Lys Phe Phe His Arg Thr Cys Lys Cys Thr Gly Asn Phe Ala Gly Tyr Asn Cys Gly Asp Cys Lys Phe Gly Trp Thr Gly Pro Asn Cys Glu Arg Lys Lys Pro Pro Val Ile Arg Gln Asn Ile His Ser Leu Ser Pro Gln Glu Arg Glu Gln Phe Leu Gly Ala Leu Asp Leu Ala Lys Lys Arg Val His Pro Asp Tyr Val Ile Thr Thr Gln His Trp Leu Gly Leu Leu Gly Pro Asn Gly Thr Gln Pro Gln Phe Ala Asn Cys Ser Val Tyr Asp Phe Phe Val Trp Leu His Tyr Tyr Ser Val Arg Asp Thr Leu Leu Gly Pro Gly Arg Pro Tyr Arg Ala Ile Asp Phe Ser His Gln Gly Pro Ala Phe Val Thr Trp His Arg Tyr His Leu Leu Cys Leu Glu Arg Asp Leu Gln Arg Leu Ile Gly Asn Glu Ser Phe Ala Leu Pro Tyr Trp Asn Phe Ala Thr Gly Arg Asn Glu Cys Asp Val Cys Thr Asp Gln Leu Phe Gly Ala Ala Arg Pro Asp Asp Pro Thr Leu Ile Ser Arg Asn Ser Arg Phe Ser Ser Trp Glu Thr Val Cys Asp Ser Leu Asp Asp Tyr Asn His Leu Val Thr Leu Cys Asn Gly Thr Tyr Glu Gly Leu Leu Arg Arg Asn Gln Met Gly Arg Asn Ser Met Lys Leu Pro Thr Leu Lys Asp Ile Arg Asp Cys Leu Ser Leu Gln Lys Phe Asp Asn Pro Pro Phe Phe Gln Asn Ser Thr Phe Ser Phe Arg Asn Ala Leu Glu Gly Phe Asp Lys Ala Asp Gly Thr Leu Asp Ser Gln Val Met Ser Leu His Asn Leu Val His Ser Phe Leu Asn Gly Thr Asn Ala Leu Pro His Ser Ala Ala Asn Asp Pro Ile Phe Val Val Leu His Ser Phe Thr Asp Ala Ile Phe Asp Glu Trp Met Lys Arg Phe Asn Pro Pro Ala Asp Ala Trp Pro Gln Glu Leu Ala Pro Ile Gly His Asn Arg Met Tyr Asn Met Val Pro Phe Phe Pro Pro Val Thr Asn Glu Glu Leu Phe Leu Thr Ser Asp Gln Leu Gly Tyr Ser Tyr Ala Ile Asp Leu Pro Val Ser Val Glu Glu Thr Pro Gly Trp Pro Thr Thr Leu Leu Val Val Met Gly Thr Leu Val Ala Leu Val Gly Leu Phe Val Leu Leu Ala Phe Leu Gln Tyr Arg Arg Leu Arg Lys Gly Tyr Thr Pro Leu Met Glu Thr His Leu Ser Ser Lys Arg Tyr Thr Glu Glu Ala

FIGURE 6D

gp100 and gp100M

```
1        MDL VLKRCLLHLA VIGALLAVGA TKVPRNQDWL GVSRQLRTKA WNRQLYPEWT
2        *** ********** ********** ********** ********** **********

1 EAQRLDCWRG GQVSLKVSND GPTLIGANAS FSIALNFPGS QKVLPDGQVI WVNNTIINGS
2 ********** ********** ********** ********** ********** **********

1 QVWGGQPVYP QETDDACIFP DGGPCPSGSW SQKRSFVYVW KTWGQYWQFL GGPVSGLSIG
2 ********** ********** ********** ********** ********V* **********

1 TGRAMLGTHT MEVTVYHRRG SRSYVPLAHS SSAFTITDQV PFSVSVSQLR ALDGGNKHFL
2 ********** ********** ********** ******M*** ********** **********

1 RNQPLTFALQ LHDPSGYLAE ADLSYTWDFG DSSGTLISRA LVVTHTYLEP GPVTAQVVLQ
2 ********** ********** ********** ********** ********** ****V*****

1 AAIPLTSCGS SPVPGTTDGH RPTAEAPNTT AGQVPTTEVV GTTPGQAPTA EPSGTTSVQV
2 ********** ********** ********** ********** ********** **********

1 PTTEVISTAP VQMPTAESTG MTPEKVPVSE VMGTTLAEMS TPEATGMTPA EVSIVVLSGT
2 ********** ********** ********** ********** ********** **********

1 TAAQVTTTEW VETTARELPI PEPEGPDASS IMSTESITGS LGPLLDGTAT LRLVKRQVPL
2 ********** ********** ********** ********** ********** **********

1 DCVLYRYGSF SVTLDIVQGI ESAEILQAVP SGEGDAFELT VSCQGGLPKE ACMEISSPGC
2 ********** ********** ********** ********** ********** **********

1 QPPAQRLCQP VLPSPACQLV LHQILKGGSG TYCLNVSLAD TNSLAVVSTQ LIMPGQEAGL
2 ********** ********** ********** ********** ********** **********

1 GQVPLIVGIL LVLMAVVLAS LIYRRRLMKQ DFSVPQLPHS SSHWLRLPRI FCSCPIGENS
2 ********** ********** ********** ********** ********** **********

1 PLLSGQQV2 ********
```

Key
*=identical amino acid residue
1=gp100
2=gp100M

FIGURE 6E

MART-1

Met Pro Arg Glu Asp Ala His Phe Ile Tyr Gly Tyr Pro
Lys Lys Gly His Gly His Ser Tyr Thr Thr Ala Glu Glu
Ala Ala Gly Ile Gly Ile Leu Thr Val Ile Leu Gly Val
Leu Leu Leu Ile Gly Cys Trp Tyr Cys Arg Arg Arg Asn
Gly Tyr Arg Ala Leu Met Asp Lys Ser Leu His Val Gly
Thr Gln Cys Ala Leu Thr Arg Arg Cys Pro Gln Glu Gly
Phe Asp His Arg Asp Ser Lys Val Ser Leu Gln Glu Lys
Asn Cys Glu Pro Val Val Pro Asn Ala Pro Pro Ala Tyr
Glu Lys Leu Ser Ala Glu Gln Ser Pro Pro Pro Tyr Ser
Pro

FIGURE 6F

MAGE-1

Met Ser Asp Asn Lys Lys Pro Asp Lys Ala His Ser Gly Ser Gly Gly
Asp Gly Asp Gly Asn Arg Cys Asn Leu Leu His Arg Tyr Ser Leu Glu
Glu Ile Leu Pro Tyr Leu Gly Trp Leu Val Phe Ala Val Val Thr Thr
Ser Phe Leu Ala Leu Gln Met Phe Ile Asp Ala Leu Tyr Glu Glu Gln
Tyr Glu Arg Asp Val Ala Trp Ile Ala Arg Gln Ser Lys Arg Met Ser
Ser Val Asp Glu Asp Glu Asp Asp Glu Asp Asp Glu Asp Asp Tyr Tyr
Asp Asp Glu Asp Asp Asp Asp Asp Ala Phe Tyr Asp Asp Glu Asp Asp
Glu Glu Glu Glu Leu Glu Asn Leu Met Asp Asp Glu Ser Glu Asp Glu
Ala Glu Glu Glu Met Ser Val Glu Met Gly Ala Gly Ala Glu Glu Met
Gly Ala Gly Ala Asn Cys Ala Cys Val Pro Gly His His Leu Arg Lys
Asn Glu Val Lys Cys Arg Met Ile Tyr Phe Phe His Asp Pro Asn Phe
Leu Val Ser Ile Pro Val Asn Pro Lys Glu Gln Met Glu Cys Arg Cys
Glu Asn Ala Asp Glu Glu Val Ala Met Glu Glu Glu Glu Glu Glu Glu
Glu Glu Glu Glu Glu Glu Glu Met Gly Asn Pro Asp Gly Phe Ser Pro

FIGURE 6G

MAGE-3

mpleqrsqhc kpeeglearg ealglvgaqa pateeqeaas ssstlvevtl gevpaaespd
ppqspqgass lpttmnyplw sqsyedssnq eeegpstfpd lesefqaals rkvaelvhfl
llkyarepv tkaemlgsvv gnwqyffpvi fskassslql vfgielmevd pighlyifat
clglsydgll gdnqimpkag lliivlaiia regdcapeek iweelsvlev fegredsilg
dpkklltqhf vqenyleyrq vpgsdpacye flwgpralve tsyvkvlhhm vkisggphis
ypplhewvlr egee

FIGURE 6H
B7.1

```
mghtrrqgts pskcpylnff qllvlaglsh fcsgvihvtk evkevatlsc ghnvsveela
qtriywqkek kmvltmmsgd mniwpeyknr tifditnnls ivilalrpsd egtyecvvlk
yekdafkreh laevtlsvka dfptpsisdf eiptsnirri icstsggfpe phlswlenge
elnainttvs qdpetelyav sskldfnmtt nhsfmcliky ghlrvnqtfn wnttkqehfp
dnllpswait lisvngifvi ccltycfapr crerrrnerl rresvrpv
```

FIGURE 6I
LFA-3

```
mvagsdagra lgvlsvvcll hcfgfiscfs qqiygvvygn vtfhvpsnvp lkevlwkkqk
dkvaelense frafssfknr vyldtvsgsl tiynltssde deyemespni tdtmkfflyv
leslpsptlt caltngsiev qcmipehyns hrglimyswd cpmeqckrns tsiyfkmend
lpqkiqctls nplfnttssi ilttcipssg hsrhryalip iplavittci vlymngilkc
drkpdrtnsn
```

FIGURE 6J
ICAM-1*

```
mapssprpal pallvllgal fpgpgnaqts vspskvilpr ggsvlvtcst scdqpkllgi
etplpkkell lpgnnrkvye lsnvqedsqp mcysncpdgq staktfltvy wtpervelap
lpswqpvgkn ltlrcqvegg apranltvvl lrgekelkre pavgepaevt ttvlvrrdhh
ganfscrtel dlrpqglelf entsapyqlq tfvlpatppq lvsprvlevd tqgtvvcsld
glfpvseaqv hlalgdqrln ptvtygndsf sakasvsvta edegtqrltc avilgnqsqe
tlqtvtiysf papnviltkp evsegtevtv kceahprakv tlngvpaqpl gpraqlllka
tpedngrsfs csatlevagq lihknqtrel rvlygprlde rdcpgnwtwp ensqqtpmcq
awgnplpelk clkdgtfplp igesvtvtrd legtylcrar stqgevtrev tvnvlsprye
iviitvvaaa vimgtaglst ylynrqrkik kyrlqqaqkg tpmkpntqat pp
```

*mature sequence begins at residue 28 (q)